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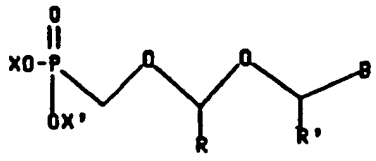
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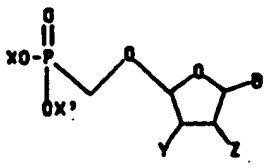
(54) Nucleoside analogs.

(57) Compounds of the following formulas which have anti-tumor and anti-viral activity and are especially useful in treating viral infections, their compositions and use.
A phosphonomethoxymethyoxymethyl purine/pyrimidine derivative of the formula



wherein X and X' are the same or different and are hydrogen or alkyl.
R and R' are the same or different and are hydrogen, alkyl, hydroyalkyl or R"CO-where R" is an alkyl and B is a purine or pyrimidine base.
A 4'-phosphonomethoxytetrahydrofuranyl-1'-purine-pyrimidine of the formula

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wherein X and X′ are the same or different and are hydrogen or alkyl,
Y and Z are the same of different and are hydrogen hydroxyl or alkyl or Y + Z is an alkenyl, an epoxide or cyclopropyl, and
B is a purine or pyrimidine base.

NUCLEOSIDE ANALOGS

BACKGROUND OF THE INVENTION

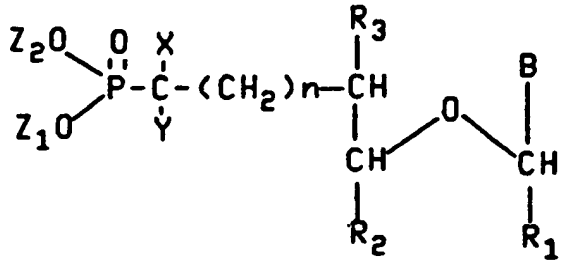
Field of the Invention

The present invention concerns nucleotide analogs and their compositions and use. In particular, the invention concerns antiviral (including antiretroviral) and antitumor phosphonomethoxymethyloxymethyl purine/pyrimidine derivatives and 4′-phosphonomethoxytetrahydrofuranyl-1′-purine/pyrimidine derivatives.

Background Information

Infectious viral diseases are recognized as an important medical problem. Progress against infectious viral disease requires the development of drugs with delective antiviral activity while remaining benign to normal cell lines. A number of antiviral agents currently under study which seem to possess some selectivity are nucleoside analogs. In general, these compounds are structural analogs of the naturally occurring nucleosides. Structural modification in either the purine or pyrimidine base nucleus and/or the saccharide component results in a synthetically modified nucleoside derivative which, when incorporated into a viral nucleic acid forming process, acts to disrupt further synthesis of viral nucleic acid. Effectiveness of these antiviral agents depends on selective conversion by viral enzymes, but not by host enzymes, to the corresponding nucleotide analog which is then converted to the triphosphate and incorporation into viral nucleic acid occurs. A problem with this antiviral strategy has been the emergence of certain viral strains whose enzymes poorly promote phosphorylation of the nucleoside analogs. To circumvent this problem, intact nucleotide analogs appear to be potentially quite useful as antivirals for incorporation into viral nucleic acid.

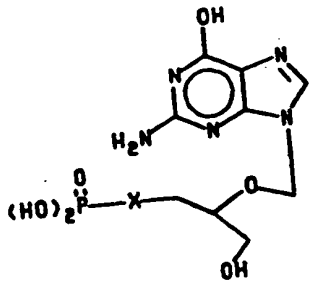
Reist and Strum in PCT/US 84/00737, published December 6, 1984, disclosed new phosphonic acid analogs of nucleoside phosphates which are useful as antivirals for incorporation into viral DNA. The structural formula for these compounds is shown below as 1′.



1′

In the Reist and Sturm compounds, B is a purine or pyrimidine base: R_1 and R_2 together complete a beta-pentofuranose sugar or R_1 is H and R_2 is H or hydroxmethyl; R_3 is H or OH: X is H, OH or together with Y is carbonyl oxygen and Y can also be H; Z_1 and Z_2 are H or alkyl.

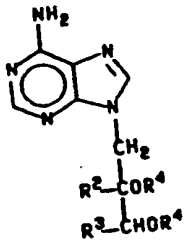
Similarly, synthesis and anti-Herpes-Virus activity of phosphate and phosphonate derivatives of 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (Formula 2′ was disclosed by Prisbe, et al., in J. Med. Chem., 1986, 29, 671.



2'

Other phosphonate nucleotide analogs of the Formula 2' type wherein X = CH_2 have been described by R. M. Riggs et al., Nucleosides and Nucleotides, 8(5&6, 1119-1120 (1989); D.H.R. Bouton, et al., Tetrahedron Letters, Vol. 30, No. 37, pp 4969-4972 (1972); and H. Tanaka, et al., Tetrahedron Letters, 30, 2567-2570 (1989).

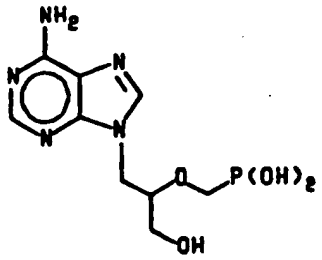
Adenine phosphonic analogs (Formula 3') and their syntheses are disclosed in the UK Patent Application of Holy, et al., GB 2,134,907A published 8/22/84.



3'

In formula 3', R_2 and R_3 are H or together complete a ribonucleoside ring; and both R_4 are alternately a hydrogen and $-CH_2P(O)(OH)_2$ group.

A preferred example of one of these compounds, known as (S)-HPMPA (Formula 4') was disclosed by DeClercq, et al., in Nature, 1986, 323, pp. 464-467 and earlier by Holy, et al., Nucleic Acids Research Symposium Series No. 14, 1984, pp. 277-278. Phosphonate compounds which are HPMPA analogs described in South African Patent 1987/8607. In applicant's hands, (S)-HPMPA is only slightly active i inoculated with Herpes simplex virus - 2. In a 21 day protocol 30% of a group of animals treated i mg/kg/day of (S)-HPMPA survived.



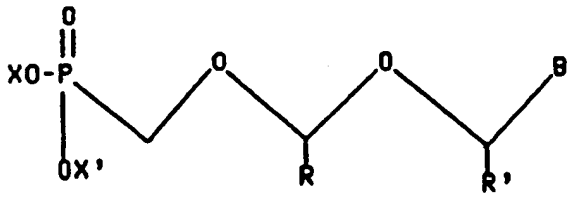
4'

There is no teaching contained in these references, or a suggested combination thereof, which would make obvious the compounds, compositions, and uses involved in the present invention.

SUMMARY OF THE INVENTION

Phosphonomethoxymethoxymethyl purine and pyrimidine derivatives, 4'-phosphonomethoxytetrahydro-2-fur-yl-9-purine and 1-pyrimidine derivatives, phosphonomethoxymethoxymethyl 9-purine and 1-pyrimidine derivatives having a cyclic phosphonate group and 4'-phosphonomethoxytetrahydro-2-fur-yl-9-purine and 1-pyrimidine derivatives having a cyclic phosphonate group have been synthesized and found to possess useful antiviral and anti tumor activity.

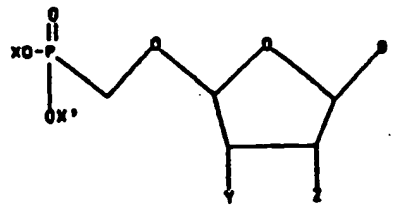
The present invention concerns a phosphonomethoxymethoxymethyl purine/pyrimidine derivative of the formula



(I)

wherein X and X' are the same or different and are hydrogen or alkyl having 1 to 6 carbon atoms, R and R' are the same or different and are hydrogen, alkyl having 1 to 6 carbon atoms, hydroxyalkyl with 1 to 6 carbon atoms, alkanoyl having 2 to 7 carbon atoms, and B is a 9-substituted purine or 1-substituted pyrimidine base selected from the group consisting of xanthine, substituted xanthine, for example, hypoxanthine, quanine, substituted guanine, for example, 8-bromoguanine, 8-chloroguanine, 8-aminoguanine, 8-hydrazinoguanine, 8-hydroxyguanine, 8-methylguanine, 8-thioguanine and 3-deazaguanine, purine, substituted purine, for example, 2-aminopurine, 2,6-diaminopurine, cytosine, substituted cytosine, for example, 5-ethylcytosine and 5-methylcytosine, thymine, uracil, 5-substituted uracil, for example, 5-chlorouracil, 5-bromouracil, 5-ethyluracil, 5-iodouracil, 5-propyluracil and 5-vinyluracil, adenine and substituted adenine, for example, 3-deazaadenine, and pharmaceutically acceptable salts thereof.

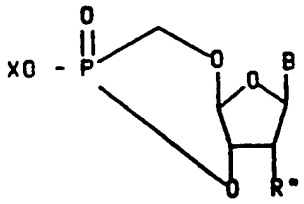
The present invention also concerns a 4'-phosphonomethoxytetrahydro(or dihydro)fur-2-yl-purine or pyrimidine derivative of the formula



(II)

wherein X and X' are the same or different and are hydrogen or alkyl having 1 to 6 carbon atoms, the broken line represents an optional double bond,
Y and Z are the same or different and are unsubstituted or substituted alkyl with 1 to 6 carbon atoms or together they constitute an oxygen atom or methylene group in which event the broken line is a single bond, and
B is a 9-substituted purine or a 1-substituted pyrimidine base selected from the group consisting of xanthine, substituted xanthine, for example, hypoxanthanine, guanine, substituted guanine, for example, 8-bromoguanine, 8-chloroguanine, 8-methylguanine and 8-thioguanine and 3-deazaguanine, purine, substituted purine, for example, 2-aminopurine, 2,6-diaminopurine, cytosine, substituted cytosine, for example, 5-ethylcytosine and 5-methylcytosine, thymine, uracil, 5-substituted uracil, for example, 5-chlorouracil, 5-bromouracil, 5-ethyluracil, 5-iodouracil, 5-propyluracil and 5-vinyluracil, adenine and substituted adenine, for example, 3-deazaadenine, and pharmaceutically acceptable salts thereof.

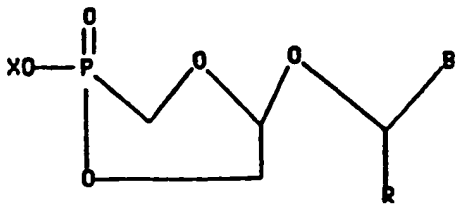
The invention also concerns to a 4'-phosphonomethoxytetrahydrofur-2-yl-purine or pyrimidine derivative having a cyclic phosphonate group of the formula



(III)

wherein X is hydrogen or alkyl with 1 to 6 carbon atoms,
R" is H or OH
and B is a 9-substituted purine or a 1-substituted pyrimidine base selected from the group consisting of xanthine, substituted xanthine, for example, hypoxanthine, guanine, substituted guanine, for example, 8-bromoguanine, 8-chloroguanine, 8-aminoguanine, 8-hydrazinoguanine, 8-hydroxyguanine, 8-methylguanine, 8-thioguanine and 3-deazaguanine, purine, substituted purine, for example, 2-aminopurine, 2,6-diaminopurine, cytosine, substituted cytosine, for example, 5-ethylcytosine and 5-methylcytosine, thymine, uracil, 5-substituted uracil, for example, 5-chlorouracil, 5-bromouracil, 5-ethyluracil, 5-iodouracil, 5-propyluracil and 5-vinyluracil, adenine and substituted adenine, for example, 3-deazaadenine,
and pharmaceutically acceptable salts thereof.

The invention is further directed to a phosphonomethoxymethoxymethyl-9-substituted purine or 1-substituted pyrimidine derivatives having a cyclic phosphonate group of the formula

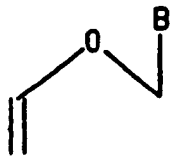


(IV)

wherein X is hydrogen, alkyl with 1 to 6 carbon atoms,
R is hydrogen, alkyl with 1 to 6 carbon atoms or alkanoyl having 2 to 7 carbon atoms, and B is a purine or

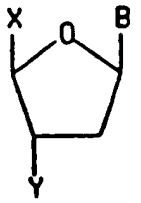
pyrimidine base selected from the group consisting of xanthine, substituted xanthine, for example, hypoxanthine, guanine, substituted guanine, for example, 8-bromoguanine, 8-chlorogranine, 8-aminoguanine, 8-hydrazinoguanine, 8-hydroxyguanine, 8-methylguanine, 8-thioguanine and 3-deazaguanine, purine, substituted purine, for example, 2-aminopurine, 2,6-diaminopurine, cytosine, substituted cytosine, for example, 5-ethylcytosine and 5-methylcytosine, thymine, uracil, 5-substituted uracil, for example, 5-chlorouracil, 5-bromouracil, 5-ethyluracil, 5-iodouracil, 5-propyluracil and 5-vinyluracil, adenine and substituted adenine, for example, 3-deazaadenine, are pharmaceutically acceptable salts thereof.

The present invention also concerns the following intermediates:



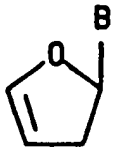
(V)

, wherein B is a 9-substituted purine or a 1-substituted pyrimidine base selected from the group consisting of xanthine, substituted xanthine, for example, hypoxanthine, guanine, substituted guanine, for example, 8-bromoguanine, 8-chloroguanine, 8-aminoguanine, 8-hydrazinoguanine, 8-hydroxyguanine, 8-methylguanine, 8-thioguanine and 3-deazaguanine, purine, substituted purine, for example, 2-aminopurine, 2,6-diaminopurine, cytosine, substituted cytosine, for example, 5-ethylcytosine and 5-methylcytosine, thymine, uracil, 5-substituted uracil, for example, 5-chlorouracil, 5-bromouracil, 5-ethyluracil, 5-iodouracil, 5-propyluracil and 5-vinyluracil, adenine and substituted adenine, for example, 3-deazaadenine;



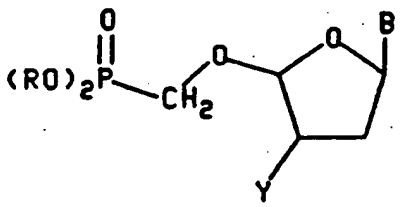
(VI)

, wherein X is a halogen, for example, chlorine, bromine, iodine or fluorine,
Y is phenylthio, phenylseleno or a halogen atom, for example, chlorine, bromine, iodine or fluroine, and B is a 9-substituted purine or 1-substituted pyrimidine base selected from the group consisting of xanthine, substituted xanthine, for example, hypoxanthine, guanine, substituted guanine, for example, 8-bromoguanine, 8-chloroguanine, 8-aminoguanine, 8-hydrazinoguanine, 8-hydroxyguanine, 8-methylguanine, 8-thioguanine and 3-deazaguanine, purine, substituted purine, got rcsmplr, 3-aminopurine, 2,6-diaminopurine, cytosine, substituted cytosine, for example, 5-ethylcytosine and 5-methylcytosine, thymine, uracil, 5-substituted uracil, for example, 5-chlorouracil, 5-bromouracil, 5-ethyluracil, 5-iodouracil, 5-propyluracil and 5-vinyluracil, adenine and substituted adenine, for example, 3-deazaadenine;



VII

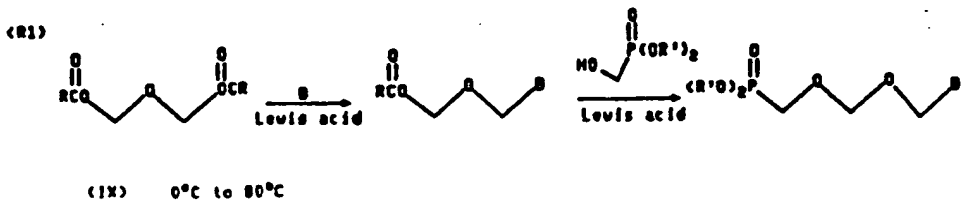
. wherein B is guanine, substituted guanine, for example, 8-bromoguanine, 8-chloroguanine, 8-aminoguanine, 8-hydrazinoguanine, 8-hydroxyguanine, 8-methylguanine, 8-thioguanine and 3-deazaguanine, cystosine or substituted cytosine, for example, 5-ethylcytosine and 5-methylcytosine; and



(VIII)

wherein Y is a halogen, for example chlorine, fluorine, bromine or iodine, phenylthio, or phenylselano, R is hydrogen or alkyl with 1 to 6 carbon atoms and B is a purine or pyrimidine base selected from the group consisting of xanthine, substituted xanthine, for example, hypoxanthine, guanine, substituted guanine, for example, 8-bromoguanine, 8-chloroguanine, 8-aminoguanine, 8-hydrazinoguanine, 8-hydroxyguanine, 8-methylguanine, 8-thioguanine and 3-deazaguanine, purine, substituted purine, for example, 2-aminopurine, 2,6-diaminopurine, cytosine, substituted cytosine, for example, 5-ethylcytosine and 5-methylcytosine, thymine, uracil, 5-substituted uracil, for example, 5-chlorouracil, 5-bromouracil, 5-ethyluracil, 5-iodouracil, 5-propyluracil and 5-vinyluracil, adenine and substituted adenine, for example, 3-deazaadenine.

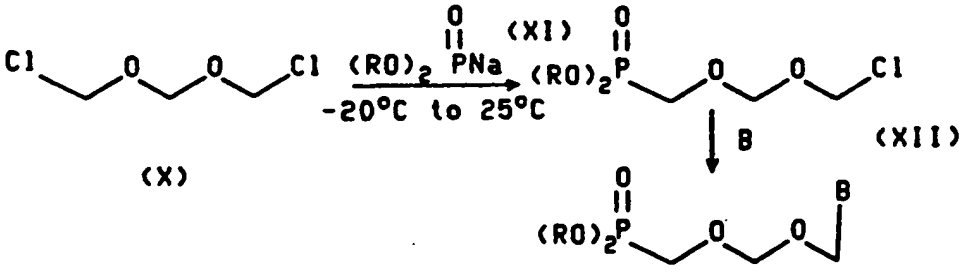
The present invention further relates to the following processes:



(IX) 0°C to 80°C

wherein R is an alkyl having 1 to 6 carbon atoms or an unsubstituted aryl or an aryl substituted by a substituent such as a halogen, e.g., bromine or chlorine, nitro, alkyl having 1 to 6 carbon atoms or an alkoxy having 1 to 6 carbon atoms, B is a silylated purine or pyrimidine base, and R′ is hydrogen or alkyl with 1 to 6 carbon atoms; preferably the molar ratio of compound (IX) to B is 1:1; the corresponding substituted derivatives (R and R′ in formula I other than hydrogen) are obtained in an analogous manner.

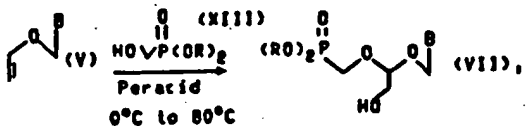
(R2)



(X) (XII)

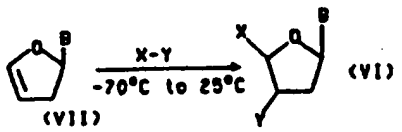
wherein R is an alkyl having 1 to 6 carbon atoms and B is a purine or pyrimidine base; preferably compound (X) is 5 to 10 times in excess of compounds (XI) and the preferred molar ratio of compound (XII) to B is 1:1, the corressponding substituted derivatives (R and R′ in formula I other than hydrogen) are obtained in an analogous manner.

(R3)



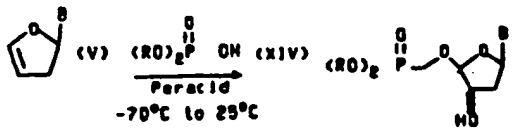
wherein compound (XIII) is preferably in a 5 to 10 times excess of compound (V);

(R4)



wherein X-Y is a halogen,e.g., Br_2, Cl_2, phenyl-Se-Z, phenyl-S-Z (wherein Z = halogen) and B is a purine or pyrimidine base; preferably the molar ratio of compound (VII) to X-Y is 1:1;

(R5)



wherein R is hydrogen or alkyl with 1 to 6 carbon atoms; preferably compound (XIV) is 5 to 10 times in excess of compound (V).

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention can exist as optical isomers and both racemic and diasteromeric mixtures of these isomers which may exist for certain compounds, as well as the individual optical isomers are all within the scope of the present invention. While the racemic mixtures can be separated into their individual isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substrates; in most instances, for the compounds of the present invention, the preferred optical isomer can be synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

As indicated above, the present invention also pertains to pharmaceutically acceptable non-toxic salts of these compounds, containing, for example, Na^+, Li^+, K^+, Ca^{++} and Mg^{++}. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with the acid anion moiety of the phosphonic acid group. Metal salts can be prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which can be prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipatated from the solution of a more soluble salt by addition of the suitable metal compound. In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g., HCl, HBr, H_2SO_4 or organic sulfonic acids, with basic centers of the purine, specifically guanine, or pyrimidine base. Finally, it is to be understood that compounds of the present invention in their un-ionized, as well as

zwitterionic form, and/or in the form, of solvates are also considered part of the present invention.

Compounds of the present invention also exist in subclasses, with two broad subclasses being those wherein B is either a purine or a pyrimidine base. Of these broad subclasses there are preferred classes wherein the purine base is a guanine or a substituted guanine moiety and where the pyrimidine bases are either thymine or cytosine. The most preferred class of compounds are those wherein B is guanine or substituted guanine.

Compounds of the present invention may also be subclassed according to the structure of the phosphonate moiety. These classes are comprised of the diester, the monoester, and the diacid. Preferred subclasses of the phosphonate moiety are the monoester and the diacid.

The compounds of this invention, including the physiologically acceptable salts thereof, have desirable antiviral and antitumor activity. They exhibit activity against viruses, for example, Herpes Simplex virus I, Herpes Simplex virus II, cytomegalovirus, Varicella Zoster virus, influenza virus, vaccinia, polio, rubella, small pox, cowpox, Epstein-Barr virus, measles virus, human respiratory virus, papillomavirus and sinbis virus, just to mention a few and also against retroviruses, for example, human immunodeficiency virus (HIV). The inventive compounds also have an antitumor effect. They are active against murine leukemia P388 and other experimental tumors.

As mentioned above, the compounds of the present invention are useful active ingredients in human and veterinary medicine for the treatment and prophylaxis of diseases caused by retroviruses. Examples of fields of indication in human medicine regarding retroviruses are as follows:

(1) the treatment or prophylaxis of human retrovirus infections;

(2) the treatment or prophylaxis of diseases caused by HIV (virus of human immune deficiency; previously called HTLV III/LAV or AIDS) and the stages associated therewith such as ARC (AIDS related complex) and LAS (lymph adenopathy syndrome) and the immune weakness and encephalopathy caused by this retrovirus;

(3) the treatment or prophylaxis of HTLV I infection or HTLV II infection;

(4) the treatment or prophylaxis of the AIDS carrier state (AIDS transmitter state); and

(5) the treatment or prophylaxis of diseases caused by hepatitis B virus.

Examples of indications in veterinary medicine are as follows:

(1) Maedivisna (in sheep and goats),

(2) progressive pneumonia virus (PPV) (in sheep and goats),

(3) caprine arthritis encephalitis virus (in sheep and goats),

(4) Zwoegerziekte virus (in sheep),

(5) infectious virus of anemia (of the horse), and

(6) infections caused by cat leukemia virus.

For use against viral infections and against tumors, the compounds of this invention can be formulated into pharmaceutical preparations. Such preparations are composed of one or more of the inventive compounds in association with a pharmaceutically acceptable carrier. The reference Remington's Pharmaceutical Sciences, 17th Edition by A.R. Gennaro (Mack Publishing Company, 1985) discloses typical carriers and methods of preparation.

For antiviral purposes, the compounds may be administered topically or systemically to warn blooded animals, e.g., humans. For antitumor use, systemic, and preferably, parenteral administration is employed. By systemic administration is intended, oral, rectal, and parenteral (i.e., intramuscular, intravenous, subcutaneous and nasal) routes. Generally, it will be found that when a compound of the present invention is administered orally, a larger quantity of the reactive agent is required to produce the same effect as the smaller quantity given parenterally. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level that will produce effective antiviral or antitumor effect without causing any harmful or untoward side effects.

Therapeutically and prophylactically the instant compounds are given as pharmaceutical compositions comprised of an effective antiviral or antitumor amount of a compound according to the invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, as stated hereinabove. Pharmaceutical compositions for effecting such treatment will contain a major or minor amount, e.g., from 95 to 0.5% of at least one compound of the present invention in combination with a pharmaceutical carrier, the carrier comprising one or more solid, semi-solid, or liquid diluents, fillers and formulation adjuvants which are non-toxic, inert and pharmaceutically acceptable. Such pharmaceutical compositions are preferable in dosage unit form; i.e., physically discrete units containing a predetermined amount of the drug corresponding to a fraction or multiple of the dose which is calculated to produce the desired therapeutic response. Other therapeutic agents can also be present. Pharmaceutical compositions providing from about 1 to 50 mg of the active ingredient per unit dose are preferred and are conventionally prepared as tablets,

lozenges, capsules, powders, aqueous or oily suspensions, syrups, elixirs, and aqueous solutions. Preferred oral compositions are in the form of tablets or capsules and may contain conventional excipients such as binding agents, (e.g., syrup, acacia, gelatin, sorbitol, tragacanth or polyvinylpyrrolidone), fillers (e.g., lactose, sugar, corn starch, calcium phosphate, sorbitol, or glycine), lubricants (e.g., magnesium stearate, talc, polyethylene glycol or silica), disintegrants (e.g., starch) and wetting agents (e.g., sodium lauryl sulfate). Solutions or suspensions of an inventive compound with conventional pharmaceutical vehicles are employed for parenteral compositions, such as an aqueous solution for intravenous injection or an oily suspension for intramuscular injection. Such compositions having the desired clarity, stability and adaptability for parenteral use are obtained by dissolving from 0.1% to 10% by weight of an active inventive compound in water or a vehicle comprising a polyhydric aliphatic alcohol such as glycerine, propylene glycol, and polyethylene glycol or mixtures thereof. The polyethylene glycols comprise a mixture of non-volatile, usually liquid, polyethylene glycols which are soluble in both water and organic liquids and have molecular weights from about 200 to 1500.

Considering the biological activities possessed by the compounds of the instant invention, it can be seen that these compounds have antitumor and antiviral properties, particularly suited to their use in combating viral infections or tumors. Thus, another aspect of the instant invention concerns a process for treating viral (including retroviral) infections or tumors in a mammal in need of such treatment which comprises systemic or topical administration to such mammal of an effective dose of an inventive compound or a pharmaceutically acceptable salt thereof. On the basis of testing, an effective dose could be expected to be from about 0.01 to about 30 mg/kg body weight with about 1 to about 20 mg/kg body weight a preferred dosage range. It is envisioned that for clinical antiviral application compounds of the instant invention will be administered in the same manner as for the reference drug acyclovir. For clinical applications, however, the dosage and dosage regimen must in each case be carefully adjusted, utilizing sound professional judgment and consideration of the age, weight and condition of the recipient, the route of administration and the nature and gravity of the illness. Generally a daily oral dose will comprise from about 150 to about 750 mg, preferable 250-500 mg of an inventive compound administered from one to three times a day. In some instances, a sufficient therapeutic effect can be obtained at lower doses, while in others, larger doses will be required.

In the reaction (process) (R1) described above, non-limiting examples of Lewis acids include Bf_3ether, $TiCl_4$ and BCl_3.

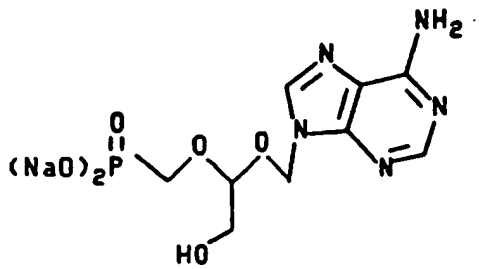
In the reactions (processes) (R3) and (R5) described above, non-limiting examples of peracids include the following: m-chloroperbenzoic acid, trifluoroperacetic acid and perbenzoic acid.

The reactions (processes) (R1) to (R5) described above are preferably conducted at atmospheric pressure and preferably conducted in the presence of a solvent, e.g., CH_3CN, CH_2Cl_2, $ClCH_2CH_2Cl$, $CHCl_3$, THF, dioxane, diethylether, benzene or toluene.

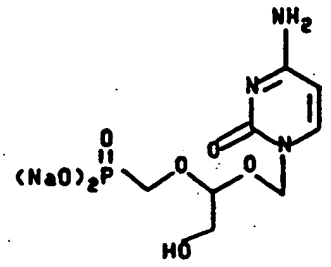
Description of the Specific Embodiments

The compounds which constitute this invention and their methods of preparation will appear more fully from a consideration of the following examples which are given for the purpose of illustration only and are not to be construed as limiting the invention in sphere or scope. In addition to the compounds described in the following examples, further compounds encompassed by the present invention are as follows:

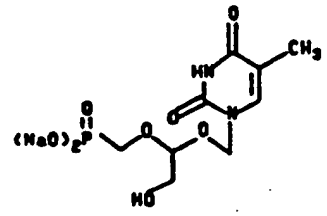
9-[(2-Hydroxy-1-phosphonomethoxyethoxy)methyl]adenine disodium salt



9-[(2-Hydroxy-1-phosphonomethoxyethoxy)methyl]cytosine disodium salt



9-[(2-Hydroxy-1-phosphonomethoxyethoxymethyl]thymine disodium salt



In the following examples, all temperatures are understood to be in degrees C when not specified. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed in parts per million (ppm) versus tetramethylsilane (TMS) as a reference standard. The relative area reported for the various shifts in the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), doublet (d), doublet of doublets (dd), triplet (t) or quartet (q). Abbreviations employed are:

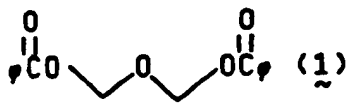
ACV (acyclovir)
BID (twice a day)
$CDCl_3$ (deuterochloroform)
DMf (dimethylformamide
DMSO-d_6 (perdeuterodimethylsulfoxide)
EMEM (Earle's Minimum Essential medium)
Et (ethyl)
HIV (human immune deficiency
HSV (Herpes simplex virus)
MuLV (murine leukemia virus)
NOE (Nuclear Overhouse Effect)
PFU (plaque forming units)
ϕ (phenyl)
TMS (trimethylsilyl)
Me (methyl)
Ac (acetyl)
Pv (pivaloyl)
Ph (phenyl)

All compounds gave satisfactory elemental analyses.

The invention will now be described with reference to the following non-limiting examples.

Examples:

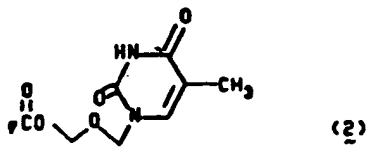
Example 1: Bisbenzoyloxymethyl ether (1)



(1)

To a suspension of sodium benzoate (5.0 g, 34.7 mmol) in DMF (70 mL) was added bischloromethyl ether (20 g, 17.3 mmol) and the mixture was heated at 70° C for 16 hours. The insoluble material was removed by filtration. The filtrate was concentrated in vacuo to give a white crystal which was recrystallized from ether-pentane: yield 4.5 g (91%); mp 39° C.
Analysis: Calc. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.92.
Found: C, 66.87; H, 4.94.
^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.66 (s, 4H), 7.75-8.05 (m,10H).

Example 2: 1-[(Benzoyloxymethyoxy)methyl]thymine (2)

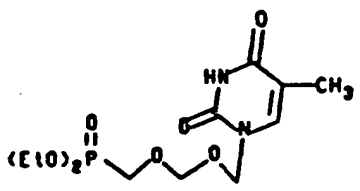


(2)

(1) A suspension of thymine (12.6 g, 0.1 mole), ammonium sulfate (300 mg) and trimethylsilyl chloride (2.5 mL) in hexamethyldisilazane (150 mL) was heated at 140° C for 16 hours under nitrogen. The volatiles were removed in vacuo at 50° C and the residual oil was dissolved in xylene (30 mL) and concentrated to dryness.

(2) To a solution of the silylated thymine in CH_2Cl_2 (200 mL) was added bisbenzoyloxymethyl ether (30 g, 0.1 mol) and trimethylsilyl trifluoromethanesulfonate (50 mL). The solution was stirred for 8 hours at 25° C under nitrogen. The reaction was diluted with ethyl acetate (400 mL) and washed with aqueous sodium carbonate, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude oily material was purified by silica gel column chromatography using CH_2Cl_2-5% MeOH as an eluent to give the title compound as white crystals: yield 14.5 g (50%); mp 141-143° C.
Analysis: Calc. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.82; N, 9.65.
Found: C, 57.59; H, 4.90; N, 9.52.
^{13}C-NMR (50.3 MHz, d_6DMSO): δ 70.779, 72.477, 72.915, 73.349, 82.985, 105.563, 123.376, 124.076, 124.368, 128.383, 134.397, 146.260, 159.451, 160.211.
1H-NMR ($CDCl_3$): δ 1.82 (s,3H), 5.38 (s, 2H), 5.62 (s, 2H), 7.10 (s,1H), 7.4-8.0 (m,5H).

Example 3: 1-[(Diethylphosphonomethoxy)methoxymethyl]thymine (3)

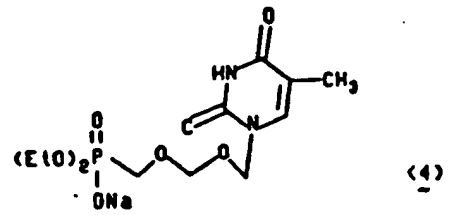


(3)

To a solution of 1-[3(benzoyloxy)methoxymethyl]thymine (2.9 g, 10 mmol) and diethylphosphonomethanol (1.85 g, 11 mmol) in benzene (180 mL) was added trimethylsilyl trifluoromethanesulfonate (0.05 mL) via a syringe under nitrogen. The solution was heated at 85° C for 20 minutes. After cooling to room temperature, ethyl acetate (50 mL) was added and washed with aqueous bicarbonate, brine

dried ($MgSO_4$), filtered and concentrated in vacuo. The resultant yellow oil was purified by silica gel column chromatography using CH_2Cl_2-5% MeOH as an eluent to give the title compound as a white oil: yield 980 mg (30%).
H^1-NMR (200 MHz, $CDCl_3$): δ 1.39 (t, J = 6.6 Hz, 6H), 1.98 (s, 3H), 3.85 (d, J = 9.9 Hz, 2H), 4.1-4.3 (m, 4H), 4.82 (s, 2H), 5.20 (s, 2H), 7.20 (s, 1H), 9.0 (broad s, 1H).

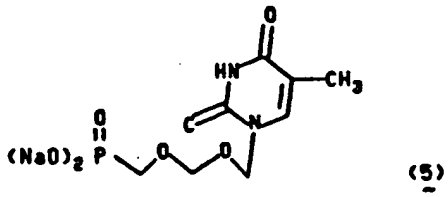
Example 4: 1-[3-(Ethylphosphonomethoxy)methyloxymethyl)]thymine sodium salt (4)



(4)

A solution of 1-[(diethylphosphonomethoxy)methoxymethyl]thymine (400 mg, 1.2 mmol) in 1N NaOH (8 mL) was stirred for 3 hours at 25° C. The solution was concentrated in vacuo and the resultant solid was purified by C-18 reverse phase column chromatography using water as an eluent under 8 psi pressure. The fractions having ultraviolet absorption were checked with HPLC, combined and lyophilized to give the title compound as a white amorphous powder: yield 220 mg (55%).
Analysis: Calc. for $C_{10}H_{16}N_2O_7PNa\ H_2O$: C, 34.48; H, 5.17; N, 8.05. Found: C, 34.92; H, 5.37; N, 8.35.
UV (H_2O): λ max 226 nm (ε = 6966).
^{13}C-NMR (50.3 MHz, D_2O): δ 11.451, 15.843, 61.067, 61.826, 63.585, 75.247, 94.631, 111.049, 141.277, 155.20, 170.907.
^1H-NMR (200 MHz, D_2O): δ 1.19 (t, J = 6.8 Hz, 3H), 1.81 (s, 3H), 3.62 (d, J = 8.9 Hz, 2H), 3.8-4.1 (m, 2H), 3.62 (s, 2H), 4.78 (s, 2H), 5.20 (s, 2H), 7.45 (s, 1H).

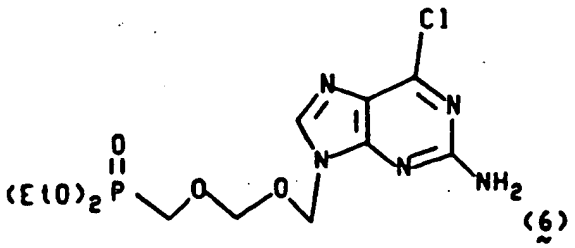
Example 5: 1-[(Phosphonomethoxy)methoxymethyl]thymine disodium salt (5)



(5)

To a solution of 1-[3'-(ethylphosphonomethoxy)methoxymethyl]thymine sodium salt (300 mg, 0.9 mmol) in dry DMF (5 mL) was added bromotrimethylsilane (1.5 mL) under nitrogen. After stirring 3 hours at 25° C, volatiles were removed in vacuo and the residue was dissolved in aqueous saturated bicarbonate and re-evaporated in vacuo to a solid foam. Purification of this material by a C-18 reverse phase column chromatography using water as eluent under 8 psi pressure and lyophilization of combined fractions gave the title compound as a white amorphous foam: Yield 140 mg (48%).
Analysis: Calcd. for $C_8H_{11}N_2O_7PNa_2$: C, 29.64; H, 3.42; N, 8.64. Found: C, 29.91; H, 3.61; N, 9.16.
UV (H_2O): λ max 266 nm (ε = 8100).
^{13}H-NMR (200 MHz, D_2O): δ 1.75 (s, 3H), 3.27 (d, J = 8.5 Hz, 2H), 4.71 (s, 2H), 5.11 (s, 2H), 7.74 (s, 1H).

Example 6: 2-Amino-6-chloro-9-[(diethylphosphonomethoxy)methoxymethyl]purine (6)

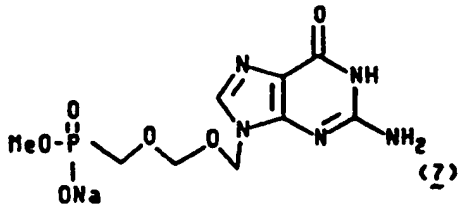


(6)

To a suspension of 60% sodium hydride in mineral oil (1.4 g, 34.5 mmol) in n-pentane (100 mL) at 0° C was added dropwise diethyl phosphate (4.4 mL, 34.5 mmol) under nitrogen. After stirring for 1 hour at 0° C, a solution of bis(chloromethoxy)methane (25 g, 172 mmol) (prepared according to the literature procedure: P.R. Strapp, J. Org. Chem., 34, 1143 (1969) in n-pentane (50 mL) was added at -70° C. The mixture was stirred for 90 minutes at 0° C, and then the solvent was evaporated under reduced pressure. The residual oil was dissolved in xylene and volatiles were removed in vacuo to give crude chloromethoxy-(diethoxyphosphonomethoxy)methane. Without further purification, this material was used for the next reaction.

To a suspension of 60% sodium hydride in mineral oil (1.4 g, 34.5 mmol) in DMF (100 mL) was added 2-amino-6-chloropurine (5.78 g, 34.2 mmol) and the mixture was stirred for 1 hour at 25° C. To the resulting yellow solution was added dropwise a solution of above chloromethoxy(diethylphosphonomethoxy)methane in DMF (20 mL) under nitrogen. After stirring 15 hours at 25° C, volatiles were removed in vacuo. The residual oil was suspended in ethyl acetate (100 mL), washed with water (30 mL), brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residual oil was chromatographed on silica gel using CH_2Cl_2-3% MeOH as an eluent to give the title compound as a colorless oil: yield 3.0 g (23%).
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.395 (t, J = 6.9 Hz, 6H), 3.850 (d, J = 9.0 Hz, 2H), 4.05-4.20 (m, 4H), 4.697 (s, 2H), 5.323 (broad s, 2H) 5.578 (s, 2H, 7.889 (s, 1H).

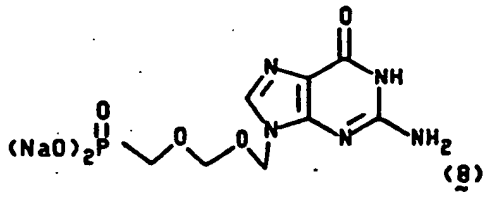
Example 7: 9-[(Methylphosphonomethoxy)methoxymethyl]guanine sodium salt (7)



(7)

To a solution of 2-amino-6-chloro-9-[3-(diethylphosphonomethoxy)methoxy-methyl] purine (325 mg, 0.84 mmol) in methanol (5 mL) was added 1N sodium methoxide in methanol (10 mL). The solution was heated at 80° C for 1 hour under nitrogen. Volatiles were removed under reduced pressure. The residual oil was then dissolved in water (10 mL) and the solution was heated at 100° C for 1 hour. The pH of the solution was carefully adjusted to 8.0 at 0° C by dropwise addition of 1N-HCl. Water was then evaporated in vacuo and the residual oil was purified by a C_{18} reverse phase column using water as an eluent to give the title compound as a white solid: yield 185 mg(60%).
Analysis: Calcd. for $C_9H_{11}N_5O_6PNa\ 4H_2O$: C, 26.13; H, 5.12; N, 16.95. Found: C, 26.05; H, 4.99; N, 16.64.
UV (H_2O): λ max 254 nm (ε = 14,372), 274 nm (ε = 9.788).
^{13}C-NMR (75.47 MHz, D_2O): δ 51.875, 60.464, 63.627, 70.005, 94.711, 94.952, 116.171, 139.925, 151.665, 154.428, 159.278.
^{1}H-NMR (300 MHz, D_2O): 3.677 (d, J = 10.3Hz, 3H), 3.620 (d, J = 9.0 Hz, 2H), 4.817 (s, 2H), 5.539 (s, 2H), 7.882 (s, 2H).

Example 8: 9-[3-(phosphonomethoxy)methoxymethyl]guanine disodium salt (8)



(8)

To a solution of 9-[(methylphosphonomethoxy)methoxymethyl]guanine (1.5 g, 4.4 mmol) in DMF (5 mL) was added bromotrimethylsilane (5 mL) under nitrogen. After stirring 3 hours at 25° C, the volatiles were removed in vacuo and the residue was neutralized to pH 8.0 by addition of aqueous saturated sodium bicarbonate. Water was then evaporated in vacuo, and the residue was purified by a C_{18} reverse phase column using water as an eluent under 8 psi pressure to give the title compound as a white powder: yield 900 mg (59%).

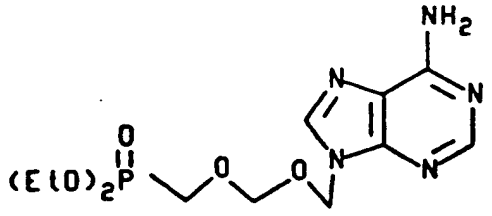
Analysis: Calcd. for $C_8H_{10}N_5O_5PNa\ 3H_2O$: C, 23.84; H, 4.01; N, 17.37. Found: C,23.99; H, 3.92; N, 17.21

UV (H_2O): λ max 252 nm (ε = 12,113), 274 nm (ε = 8,201).

^{13}C-NMR (75.47 MHz, D_2O): δ 67.016, 69.018, 70,746, 95.680, 95.831, 118.192, 141.812, 153.576, 157.386, 162.493.

^{1}H-NMR (300 MHz, D_2O): δ 3.525 (d, J = 8.9 Hz, 2H), 4.766 (s, 2H), 5.539 (s, 2H), 7.892 (s, 1H).

Example 9: 9-[(Diethylphosphonomethoxy]methoxymethyl]adenine (9)

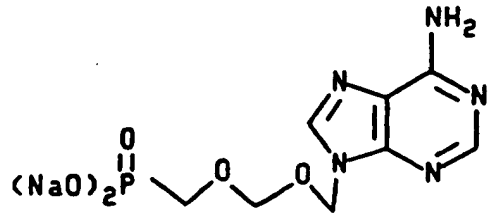


(9)

To a suspension of 60% sodium hydride in mineral oil (1.4 g, 34.5 mmol) in DMF (100 mL) was added adenine (4.7 g, 34.5 mmol) and the mixture was stirred at 80° C for 1 hour. To the resulting yellow solution was added dropwise a solution of chloromethoxy-(diethoxyphosphinolmethoxy)methane [(prepared from diethylphosphate (4.4 mL, 34.5 mmol) and bis-(chloromethoxy)methane (25 g, 172 mmol)] in DMF (20 mL) under nitrogen. After stirring at 25° C for 15 hours, volatiles were removed in vacuo, and the resulting oily residue was purified by silica gel column chromatography using CH_2Cl_2-10% MeOH as an eluent to obtain the title compound as a colorless oil: yield 6.0 g (50%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.390, (t, J = 6.7 Hz, 6H), 3.821 (d, J = 9.2 Hz, 2H), 4.05-4.18 (m, 4H), 4.785 (s, 2H), 5.690 (s, 2H), 6.20 (broad s, 2H), 7.921 (s, 1H), 8.295 (s, 1H).

Example 10: 9-[3-(Phosphonomethoxy)methoxymethyl]adenine disodium salt (10)



(10)

To a solution of 9-[(diethylphosphonomethoxy)methoxymethyl]adenine (600 mg, 1.7 mmol) in DMF (4 mL) was added bromotrimethylsilane (5 mL) under nitrogen. After stirring 3 hours at 25°C, the volatiles were removed in vacuo and the residue was neutralized to pH 8.0 by addition of aqueous saturated sodium bicarbonate. Water was then evaporated in vacuo, and the residue was purified by a C_{18} reverse phase column using water as an eluent under 8 psi pressure to give the title compound as a white powder: yield 280 mg (50%).

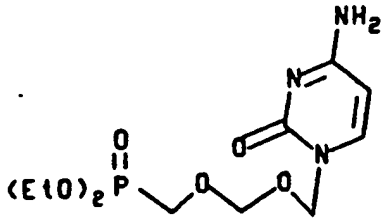
Analysis: Calcd for $C_8H_{10}N_5O_5PNa_2$ ($3H_2O$ + 0.2 mol NaCl): C, 22.08; H, 4.72; N, 16.10. Found: C, 22.15; H, 4.64; N, 16.26.

UV (H_2O): λ max 260 nm (ϵ = 12,016)

^{13}C-NMR (75.47 MHz, D_2O): δ 66.913, 68.917, 71.033, 95.729, 95.940, 120.228, 144.611, 150.754, 154.766, 157.370.

^{1}H-NMR (300 MHz, D_2O): δ 3.486 (d, J = 8.9 Hz, 2H), 4.779 (s, 2H), 5.710 (s, 2H), 8.177 (s, 1H), 8.226 (s, 1H).

Example 11: 1-[(Diethylphosphonomethoxy)methoxymethyl]cytosine (11)

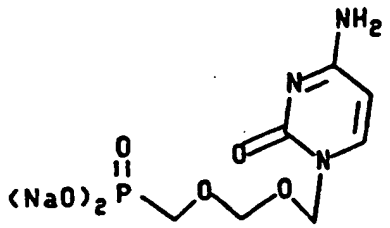


(11)

To a suspension of 60% sodium hydride in mineral oil (700 mg, 17 mmol) in DMF (50 mL) was added cytosine (1.9g, 17 mmol) and the mixture was heated at 80°C for 2 hours under nitrogen. To the resulting yellow solution was added dropwise a solution of chloromethoxy(diethylphosphonomethoxy)methane [prepared from diethylphosphate (2.4 g, 17 mmol) and bis(chloromethoxy)methane (12.5 g, 86 mmol)] in DMF (10 mL) under nitrogen. After stirring 15 hours at 25°C, the volatiles were removed in vacuo. The residue was dissolved in ethyl acetate (120 mL) and water (30 mL). The organic phase was washed with brine and dried ($MgSO_4$). After removal of the solvent in vacuo, the residual oil was chromatographed on silica gel using CH_2Cl_2-10% MeOH as an eluent to give the title compound as a white oil: yield 1.2 g (22%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.390 (t, J = 6.9 Hz, 6H), 1.90 (broad s, 2H), 3.815 (d, J = 9.0 Hz, 2H), 4.05-4.20 (m, 4H), 4.752 (s, 2H), 5.20 (s, 1H), 5.853 (d, J = 7.4 Hz, 1H), 7.312 (d, J = 7.4 Hz, 1H).

Example 12: 1-(Phosphonomethoxy)methoxymethylcytosine disodium salt (12)



(12)

To a solution of 1-[diethylphosphonomethoxy)methoxymethyl]cytosine (1.2 g, 3.7 mmol) in DMF (5 mL) was added bromotrimethylsilane (5 mL) under nitrogen. After stirring 3 hours at 25°C, the volatiles were removed in vacuo and the residue was neutralized to pH of 8.0 by the addition of aqueous saturated sodium bicarbonate. Water was then evaporated in vacuo and the residue was purified by a C_{18} reverse phase column using water as eluent under 8 psi pressure to give the title compound as a white solid: yield 460 mg (47%).

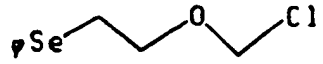
Analysis: Calcd. for $C_7H_{11}N_3O_6PNa_2$ (3 H_2O + 5% NaCl); C, 21.99; H, 4.22; N, 10.99. Found: C, 21.72; H, 4.65; N, 10.78.

UV (H_2O): λ max 268 nm (ε = 8,245)

^{13}C-NMR (75.47 MHz, D_2O): δ 66.876, 68.873, 77.710, 96.141, 96.284, 98.178, 148.355, 160.409, 162.543.

^{1}H-NMR (300MHz, D_2O): δ 3.560 (d, J = 9.0 Hz, 2H), 4.849 (s, 2H), 5.313 (s, 2H), 6.03 (d, J = 7.3 Hz, 1H), 7.714 (d, J = 7.3 Hz, 1H).

Example 13: [2-(Phenylselenyl]ethoxy]methyl chloride (13)

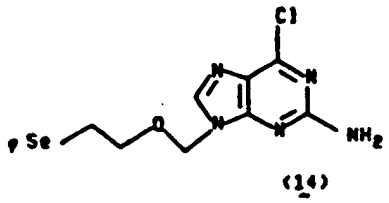


(13)

To a solution of 2-(phenylselenyl)ethanol (4.0 g, 20 mmol) [prepared according to the literature procedure: P. Rollin, V.V. Bencomo, P. Sinay, Synthesis, 13 (1984] in CH_2Cl_2 15 mL) was added paraformaldehyde (620 mg, 20 mmol). HCl gas was then bubbled into the solution at 5°C for 2 hours. The solution was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the title compound as a colorless oil in a quantitative yield.

^{1}H-NMR (300 MHZ, $CDCl_3$: δ 3.059 (t, J = 7.0 Hz, 2H), 3.882 (t, J = 7.0 Hz, 2H), 5.449 (s, 2H), 7.2-7.5 (m, 5H).

Example 14: 2-Amino-6-chloro-9-[(2-(phenylselenyl]ethoxy]methyl]purine (14)

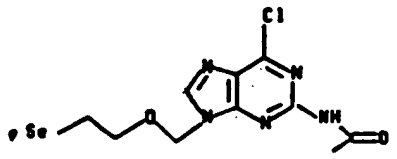


(14)

A mixture of 2-amino-6-chloropurine (20 g, 118 mmol) and ammonium sulfate (400 mg) in hexamethyldisilazane (400 mL) and chlorotrimethylsilane (6mL) was heated at 145°C for 5 hours under nitrogen. Volatiles were removed in vacuo and the residue was evaporated with xylene twice, and further dried in vacuo for 3 hours. The crude silylated 2-amino-6-chloro-purine (15 g, 72 mmol) and mercuric cyanide (15 g, 59 mmol) in benzene (900 mL) was heated at reflux for 30 minutes, then a solution of 2-(phenylselenyl)-

ethoxymethyl chloride (17 g, 68 mmol) in benzene (100 mL) was added. The mixture was refluxed for 3 hours, and then allowed to stir for 15 hours at 25° C. The reaction was diluted with CH_2Cl_2 (300 mL), and then quenched with aqueous saturated bicarbonate (2 L). The organic phase was washed with 2N potassium iodide (200 mL), dried ($MgSO_4$) and the solvents were removed in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2-5% MeOH as an eluent to provide the title compound as a slightly yellow foam: yield 15.0 g (63%).
Analysis: Calcd. for $C_{14}H_{14}N_5OClSe$ 1/2 H_2O C, 42.93; H, 3.86; N, 17.88. Found: C, 42.92: H, 3.80: N, 17.59
H^1-NMR (300 MHz, $CDCl_3$): δ 2.961 (t, J = 6.9 Hz, 2H), 3.704 (t, J - 6.9 Hz, 2H), 5.196 (broad s, 2H), 5.420 (s, 2H), 7.1-7.4 (m,5H), 7.806 (s, 1H).
^{13}C-NMR (75.47 MHz, $CDCl_3$): δ 26.041, 69.144, 72.710, 127.206, 128.653, 128.846, 131.232, 136.062, 144.946, 151.190, 151.833, 152.298.

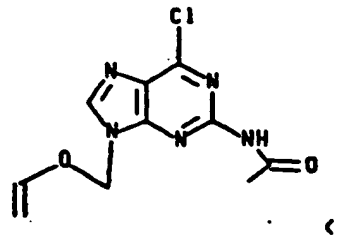
Example 15: 2-Acetamino-6-chloro-9-[(2-(phenylselenyl)ethoxy]methyl]purine (15)



(15)

A solution of 2-amino-6-chloro-9-[(2-phenylselenyl)ethoxy)methyl]purine (8 g, 21 mmol) in acetic anhydride (80 mL) was heated at 55° C for 40 hours. Volatiles were removed in vacuo and the residual oil was purified by silica gel column chromatography using CH_2Cl_2-40% EtOAc as an eluent to give the title compound as a yellow powder: yield 5.8 g (65%).
Analysis: Calcd. for $C_{15}H_{15}N_2O_2ClSe$: C, 45.25: H, 3.80; N, 16.49. Found: C, 45.12; H, 3.90; N, 16.47.
^1H-NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H), 2.961 (t, J = 6.9 Hz, 2H), 3.756 (t, J = 6.9 Hz, 2H), 5.541 (s, 2H), 7.2-7.4 (m, 5H), 8.063 (s, 1H).

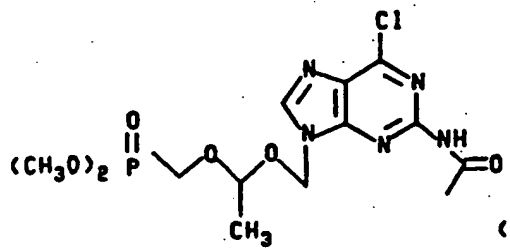
Example 16: 2-Acetamino-6-chloro-9-(vinyloxymethyl]purine (16)



(16)

To a solution of 2-acetamino-6-chloro-9-[(2-(phenylselenyl)ethoxy)methyl]purine (424 mg, 1 mmol) in methanol (20 mL) was added sodium bicarbonate (92 mg, 1.1 mmol) and sodium periodate (320 mg, 1.5 mmol). After stirring at 25° C for 30 minutes the mixture was filtered and evaporated to dryness. The residue was dissolved in dioxane (20 mL) and the solution was heated at 80° C for 20 minutes under nitrogen. The solution was evaporated in vacuo and the residual oil was chromatographed on silica gel using CH_2Cl_2-20% MeOH as an eluent to give the title compound as a slightly yellow foam: yield 220 mg (60%).
Analysis: Calcd. for $C_{10}H_{10}N_5O_2Cl$: C, 44.88; H, 3.77; N, 26.17.
Found: C, 44.57; H, 3.83; N, 25.82.

Example 17: 2-Acetamino-6-chloro-9-[(1-(dimethylphosphonomethoxy)ethoxy]methyl]purine (17)



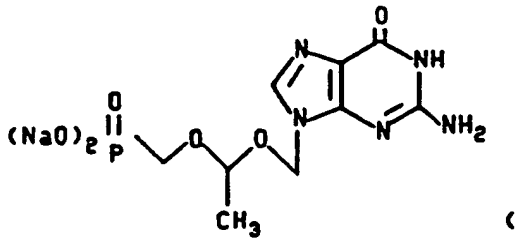
(17)

To a solution of 2-acetamino-6-chloro-9-(vinyloxy)methylpurine (2.2 g, 6.0 mmol) and dimethylphosphonomethanol (1.67 g, 12.0 mmol) in chloroform (100 mL) was added 120 mg of methanesulfonic acid. After heating at 60°C for 2 hours, the solvent was removed in vacuo and the residual oil was chromatographed on silica gel using CH_2Cl_2-10% MeOH as an eluent to give the title compound as a colorless oil: yield 1.2 g (50%).

^{13}C NMR (75.47 MHz, $CDCl_3$): 18.794, 25.054, 53.064, 53.218, 55.743, 59.056, 68.071, 99.254, 99.502, 127.921, 144.576, 151.598, 152.645, 170.299.

^1H-NMR (300 MHz, $CDCl_3$): δ 1.347 (d, J = 8.1 Hz, 3H), 2.519 (s, 3H), 3.852 (d, J = 16.2 Hz, 6H), 5.029 (q, J = 8.1 Hz, 1H), 5.648 (d, J = 15.6 Hz, 1H), 5.791 (d, J = 15.6 Hz, 1H), 7.275 (s, 1H), 8.201 (s, 1H).

Example 18: 9-[(1-(Phosphonomethoxyethoxy)methyl]guanine disodium salt (18)



(18)

To a solution of 2-acetamino-6-chloro-9-[(1-dimethylphosphonomethoxy)ethoxy)methyl]purine (1.2 g, 2.95 mmol) in methanol (5 mL) was added 1N sodium methoxide in methanol (10 mL). After stirring at 25°C for 1 hour, water (10 mL) was added and the solution was heated at 90°C for 1 hour under nitrogen. Volatiles were removed in vacuo and the residual oil was purified by C_{18} reverse phase column chromatography using water as an eluent under 8 psi pressure. Each 10 mL fraction was assayed by high pressure liquid chromatography. The combined fractions were lyophilized to give a white solid. This material was dissolved in DMF (20 mL) followed by bromotrimethylsilane (5 mL). After stirring 2 hours at 25°C, volatiles were removed in vacuo and the residue was purified by a C_{18} reverse phase column using water as an eluent under 8 psi pressure to give the title compound as white amorphous powder after lyophilization: yield 245 mg (24%).

Analysis: Calcd. for $C_9H_{12}N_5O_6PNa_2$ $4H_2O$: C, 25.78, H, 4.80; N, 16.70.

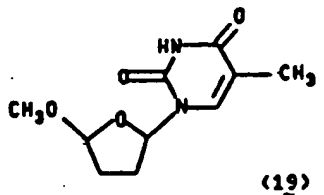
Found: C, 25.93; H, 4.44; N, 16.91.

UV (H_2O): λ max 252 nm (ϵ = 9751).

^{13}C-NMR (75.47 MHz, D_2O): δ 20.859, 64.079, 66.088, 70.423, 102.054, 102.241, 119.11, 140.287, 153.110, 162.211, 168.712.

^1H-NMR (300 MHz, D_2O): δ 1.195 (d, J = 6.3 Hz, 3H), 3.305 (dd, J = 8.9, 8.4 Hz, 1H), 3.496 (dd, J = 8.9, 8.4 Hz, 1H), 4.874, (4, J = 6.3 Hz, 1H), 5.475 (dd, J = 14.0, 11.1 Hz, 1H), 5.523 (dd, J = 14.0, 11.1 Hz, 1H), 7.790 (s, 1H).

Example 19: 1-(5-Methoxytetrahydro-2-furyl)thymine (19)



(19)

To a suspension of thymine (2.5 g, 20 mmol) in hexamethyldisilazane (30 mL) was added ammonium sulfate (50 mg) and chlorotrimethylsilane (0.5 mL) and the mixture was heated at 145 °C for 4 hours under nitrogen. The excess hexamethyldisilazane was removed at reduced pressure, and the residual oil was dissolved in xylene and evaporated in vacuo to give a colorless viscous oil. To this silylated thymine in dichloroethane (40 mL) was added 2,5-dimethoxy tetrahydrofuran (7 mL). After cooling the solution to -30 °C, tin tetrachloride (2.3 mL) was added dropwise via a syringe under nitrogen. The mixture was allowed to warm to -10 °C and was then poured into ice cold aqueous sodium bicarbonate (100 mL) and ethyl acetate (150 mL). The mixture was filtered and the organic phase was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual oil was chromatographed on silica gel using CH_2Cl_2-5% MeOH as an eluent to give the title compound as a cis/trans mixture in a ratio of 1:1 as shown by analytical HPLC and ^{1}H-NMR: yield 3.4 g (75%).

Analysis: Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.08; H, 6.24; N, 12.39.

Found: C, 52.81; N, 6.22; N, 12.38.

UV (EtOH): λmax 266 nm (ε = 9076).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.4-2.1 (m, 7H), 3.40 and 3.425 (two s, 3H), 5.20 and 5.328 (two broad s, 1h), 6.208 and 6.417 (two dd, J = 3.5, 7.0 HZ and 7.2, 7.2 Hz, 1H), 7.021 and 7.40 (broad s, 1H).

The cis/trans (19A/19B) mixture was separated by a careful silica gel column chromatography. Thus, the cis isomer 19A was eluted first with CH_2Cl_2-3% MeOH and obtained as a white needle. The X-ray crystallography and the NOE (Nuclear Overhauser Effect) nmr confirmed the cis stereochemical arrangement of 19A. mp 153-154 °C.

Analysis: Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38.

Found: C, 52.92; H, 6.20; N, 12.10.

^{13}C-NMR (75.47 MHz, $CDCl_3$): δ 12.634, 29.417, 32.157, 55.202, 105.883, 111.411, 135.952, 139.553, 150.938, 163.906.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.950 (s, 3H), 1.9-2.3 (m, 4H), 3.40 (s, 3H), 5.20 (t, J = 2.9 Hz, 1H), 6.417 (dd, J = 4.0, 7.2 Hz, 1H), 7.40 (s, 1H), 8.781 (s, 1H).

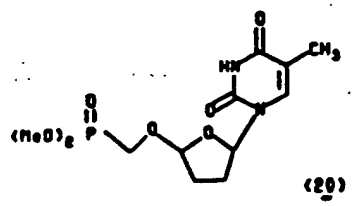
Continuing the column with CH_2Cl_2-3% MeOH, the trans isomer 19B was eluted after the cis isomer 19A and was obtained as white needles. The NOE observation of 19A was consistent with the assigned structure: mp 124-125 °C.

Analysis: Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38.

Found: C 53.10; H, 6.10; N, 12.00.

^{1}H-NMR (75.47 MHz, $CDCl_3$): δ 1.920 (s, 3H), 2.0-2.5 (m, 4H), 3.425 (s, 3H), 5.328 (dd, J = 2.5, 6.0 Hz, 1H), 6.208 (dd, J = 3.5, 7.0 Hz, 1H), 7.021 (s, 1H), 8.885 (s, 1H).

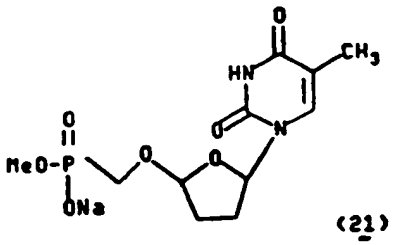
Example 20: 1-(4-Dimethylphosphonomethoxytetrahydro-2-furyl)thymine (20)



(20)

To a solution of 1-(5-methoxytetrahydro-2-furyl)thymine (5.2 g, 23 mmol) and dimethylphosphonomethanol (6.5 g, 44 mmol) in toluene was added acetic acid (5 mL) and p-toluene-sulfonic acid monohydrate (500 mg, 2.6 mmol). The solution was heated at 100° C for 2 hours and the resulting insoluble solid was removed by suction filtration. After removal of the solvent under reduced pressure, the residual oil was chromotographed on silica gel using CH_2Cl_2-5% MeOH as an eluent to give the title compound as a cis/trans mixture (6:4): yield 5.0 g (60%).
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.9-2.2 (m, 10H), 3.8-4.1 (m, 6H), 5.198, 5.445 (broad s, 0.6 and 0.4H), 6.250 (dd, J = 2.8, 7.5 Hz, 0.4H), 6.437 (t, J = 7.4 Hz, 0.6H), 7.052 (s, 0.4H), 7.405 (s, 0.6H), 9.60 (broad s, 0.6H), 7.628 (broad s, 0.4H).

Example 21: 1-(4-Methylphosphonomethoxytetrahydro-2-furyl)thymine sodium salt (21)



(21)

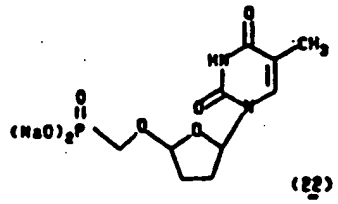
To a solution of 1-(4-dimethylphosphonomethoxytetrahydro-2-furyl)thymine (5 g, 14.6 mmol) in methanol (10 mL) was added 2N sodium hydroxide (20 mL). After stirring 2 hours at 25° C, the reaction was neutralized to pH 8.0 by addition of 3N-HCl with stirring. Water was then evaporated in vacuo and the residual oil was purified by a C_{18} reverse phase column using water as an eluent to give the title compound as a white powder. This material was shown to be a 1:1 cis/trans (21A/21B) mixture by analytical HPLC and ^{1}H-NMR: yield 3.2 g (65%).
Analysis: Calcd. for $C_{11}H_{16}N_2O_7NaP\ 2H_2O$: C, 34.92; H, 5.29; N, 7.40.
Found: C, 34.93; H, 4.99; N, 7.43.
UV (H_2O): λ max 268 nm (ε = 8668).
^{1}H-NMR (300 MHz, D_2O): δ 1.842 (s, 1.5H), 1.894 (s, 1.5H), 1.9-2.5 (m,4H), 3.571 (d, J = 9.8 Hz, 1H), 3.589 (d, J = 9.2 Hz, 1H), 3.59-3.85 (m, 2H), 5.239 (d, J = 3.5. Hz, 0.5H), 5.483 (d, J = 4.7 Hz, 0.5H), 6.198 (q, J = 2.9 Hz, 0.5H), 6.331 (t, J = 6.0 Hz, 0.5H), 7.371 (s, 0.5H), 7.561 (s, 0.5H).

The cis/trans mixture was separated by a C_{18} reverse phase column (100 time weight) using water -3% acetonitrile as an eluent under 6 psig pressure. Each 15 mL fraction was assayed by HPLC. The cis isomer 21A was eluted first and obtained as a white powder.
^{1}H-NMR(300 MHz, D_2O): δ 1.894 (s, 3H), 2.0-2.45 (m,4H), 3.571 (d, J = 9.8 Hz, 2H), 3.595 (dd, J = 7.4, 10.0 Hz, 1H), 3.781 (dd, J = 7.4, 10.8 Hz, 1H), 5.239 (d, J = 3.5 Hz, 1H), 6.331 (t, J = 6.0 Hz, 1H), 7.561 (s, 1H).

After cis-trans mixture fractions, the pure trans isomer 21B was also obtianed as a white powder.
^{1}H-NMR (300 MHz, D_2O): δ 1.842 (s, 3H), 2.0-2.5 (m, 4H), 3.589 (d, J = 9.2 Hz, 2H), 3.611 (dd, J = 9.2, 10.0 Hz, 1H), 3.840 (dd, J = 9.2, 10.0 Hz, 1H), 5.483 (d, J = 4.3 Hz, 1H), 6.198 (q, J = 2.9 Hz, 1H), 7.371 (s, 1H).

The steroechemical assignment of the cis and trans isomers was confirmed by the NOE (Nuclear Overhauser Effect) nmr.

Example 22: 1-(4-Phosphonomethoxytetrahydro-2-furyl)thymine disodium salt (22)



(22)

To a solution of 1-(4-methylphosphonotetrahydro-2-furyl)thymine sodium salt (1.2 g, 3.5 mmol) in DMF (15 mL) was added bromotrimethylsilane (10 mL) under nitrogen. After stirring 4 hours at 25 °C, the volatiles were removed in vacuo and the residual oil was neutralized to pH 8.0 by the addition of aqueous sodium bicarbonate. Water was then evaporated in vacuo, and the residue was purified by a C_{18} reverse phase column using water as an eluent under 8 psi pressure to give the title compound as a white powder: yield 857 mg (70%).

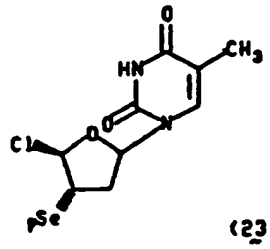
Analysis: Calcd. for $C_{10}H_{13}N_2O_7PNa_2$ $5H_2O$: C, 27.26; N, 5.20; H, 6.36.

Found: C, 27.14; H, 5.26; N, 6.03.

UV (H_2O): λ max 268 nm (ε = 7.350).

^{1}H-NMR (300 MHz, D_2O): δ 1.864 (s, 1.5H), 1.928 (s, 1.5H), 1.95-2.90 (m, 4H), 3.4-3.6 (m, 2H), 5.363 (t, J = 3.0 Hz, 0.5H), 5.56 (d, J = 4.2 Hz, 0.5H), 6.212 (dd, J = 2.7, 5.8 Hz, 0.5H), 6.321 (t, J = 3.9 Hz, 0.5H), 7.435 (s, 0.5H), 7.679 (s, 0.5H).

Example 23: 1-[2,3-Dideoxy-4-beta-chloro-3-(phenylselenyl)-beta-D-erythrofuranosyl]thymine (23)

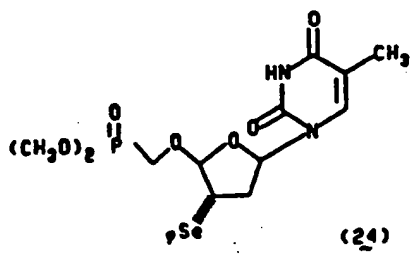


(23)

To a solution of 1-(2,3-dideoxy-3,4-didehydro-beta-D-ethyro-furanosyl)thymine (1.94 g, 10 mmol) prepared according to the literature procedure: J. Zemlicka, R. Gasser, J. V. Freisler, J. P. Norwitz, J. Amer. Chem. Soc., 94, 3213 (1972)] in CH_2Cl_2 (30 mL) was added at - 70 °C dropwise a solution of phenylselenyl chloride (1.92 g, 10 mmol) in CH_2Cl_2 (5 mL) under nitrogen. After stirring at -70 °C for 1 hour, the solvent was removed in vacuo to give the title compound as a yellowish oil. This material was used for the next reaction without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.5-2.8 (m, 2H), 4.18 (d, J = = 6.5 Hz, 1H), 6.20 (s, 1H), 6.55 (q, J -6.0, 7.5 Hz, 1H), 7.1-7.7 (m, 6H), 9.30 (broad, 1H).

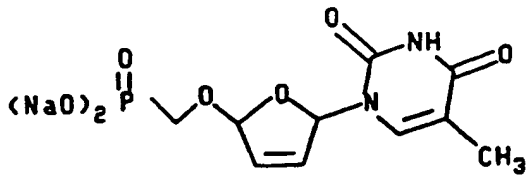
Example 24: 1-[2,3-Dideoxy-4-beta-(dimethylphosphono)methoxy-3-(phenyselenyl)beta-D-erythrofuranosyl]-thymine (24)



(24)

To a solution of 1-[2,3-dideoxy-4-chloro-3-(phenylselenyl)-beta-D-erythro-furanosyl]thymine (3.85 g, 10 mmol) and dimethoxyphosphinylmethanol (1.5 g, 11 mmol) in CH_2Cl_2 (20 mL) was added dropwise at -70° C a solution of silver perchlorate (2.3 g, 11 mmol) in CH_3CN (3 mL) over 3 minutes under nitrogen. The mixture was allowed to warm to 0° C and was then poured into aqueous saturated bicarbonate (10 mL)-brine (15 mL). The organic phase was separated after filtration and dried ($MgSO_4$). The solvents were removed under reduced pressure, and the residual oil was purified by silica gel column chromatography using CH_2Cl_2-5% MeOH as an eluent to give the title compound as a colorless oil: yield 1.3 g (31%).
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.45 (m, 2H), 3.70 (dd, J = 8.4, 8.0 Hz, 1H), 3.75 (d, J = 12.0 Hz, 6H), 3.85 (d, J = 6.9 Hz, 1H), 3.90 (dd, J = 8.4, 8.0 Hz, 1H), 5.10 (s, 1H), 6.52 (s, 1H), 7.35 (s, 1H), 8.86 (broad s, 1H).

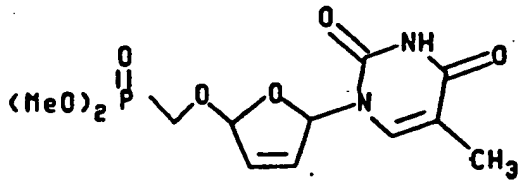
Example 25: 1-[2,3-Dideoxy-2,3-didehydro-4-phosphonomethoxy-beta-D-erythrofuranosyl]thymine disodium salt (25)



(25)

To a solution of 1-[2,3-dideoxy-4-(dimethylphosphono)methoxy-3-(phenylselenyl-beta-D-erythrofuranosyl]thymine (1.15 g, 2.76 mmol) in DMF (4 mL) was added at 5° C bromotrimethylsilane (3 mL) under nitrogen. After stirring for 4 hours at 5° C, volatiles were removed in vacuo and the residue was dissolved in aqueous saturated bicarbonate (3 mL) and evaporated again in vacuo to give a slightly yellow solid.
^{1}H-NMR (200 MHz, D_2O): δ 1.79 (s, 3H), 2.3-2.5 (m, 2H), 3.27 (1, J = 7.6, 8.4 Hz, 1H), 3.50 (1, J = 7.6, 8.4 Hz, 1H), 3.93 (d, J = 6.9 Hz, 1H), 5.23 (s, 1H), 6.0 (t, J = 6.9 Hz, 1H), 7.53 (s, 1H).
The reaction product from the above example was dissolved in water (5 mL) followed by sodium periodate (1.7 g, 8.0 mmol). After stirring for 30 minutes, the reaction mixture was heated at 80° C for 8 minutes and then filtered. The filtrate was evaporated to dryness and the residual solid was purified by a C_{18} reverse phase column chromatography using water as an eluent under 8 psi pressure. Each 15 mL fraction was assayed by high pressure liquid chromatography. Lyophilization of combined fractions gave the title compound as a white amorphous solid: yield 538 mg (50%); mp 233-237° C.
Analysis: Calcd. for $C_{10}H_{11}N_2O_7Na_2P$ H_2O: C, 32.61; H, 3.51; N, 7.61.
Found: C, 32.31; H, 3.63; N, 7.35.
^{13}C-NMR (50.3 MHz, D_2O): δ 13.921, 67.870, 69.848, 89.868, 111.242, 111.364, 113.908, 131.177, 134.655, 139.350.
^{1}H-NMR (300 MHz, D_2O): δ 1.848 (s, 3H), 3.565 (dd, J = 8.4, 8.7 Hz, 1H), 3.738 (dd, J - 8.4, 8.7 Hz, 1H), 5.987 (s, 1H), 6.180 (d, J = 6.0 Hz, 1H), 6.432 (d, J = 6.0 Hz, 1H), 6.817 (s, 1H), 7.377 (s, 1H).
UV (H_2O): λ max 266 nm (ε = 10.134).

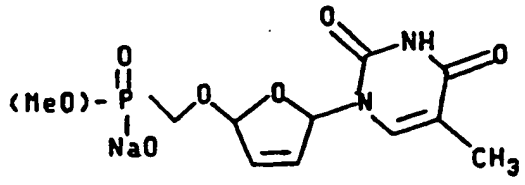
Example 26: 1-[2,3-Dideoxy-2,3-didehydro-4-beta-(dimethylphosphono)methoxy-beta-D-erythrofuranosyl]-thymine (26)



(26)

To a solution of 1-(2,3-dideoxy-4-beta-(dimethylphosphono)methoxy-3-(phenylselenyl)-beta-D-erythrofuranosyl] thymine (6.0 g, 12.2 mmol) in methanol (20 mL) was added dropwise a suspended solution of sodium bicarbonate (1.8 g, 21 mmol) and sodium periodate (3.2 g, 15 mmol) in water (20 mL). After stirring at 25° C for 1 hour, the mixture was heated at 80° C for 60 minutes. Volatiles were removed in vacuo and the residue was suspended in CH_2Cl_2 (120 mL). After removal of insoluble material, the organic phase was dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed on silica gel using CH_2Cl_2-5% MeOH as eluent to give the title compound as a white amorphous powder: yield 3.4 g (85%).
Analysis: Calcd. for $C_{12}H_{17}N_2O_7P$: C, 43.38; H, 6.16; N, 8.43.
Found: C, 43.53; H, 5.20; N, 8.26.
^{13}C-NMR (75.47 MHz, $CDCl_3$): δ 12.339, 52.889, 52.976, 53.080, 60.491, 62.738, 87.837, 108.402, 108.569, 111.653, 130.613, 131.675, 135.435, 150.480, 163.503.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.862 (s, 3H), 3.748 (d, J = 12.8 Hz, 3H), 3.814 (d, J = 12.8 Hz, 1H), 3.826 (dd, J = 8.9, 8.4 Hz, 1H), 3.902 (dd, J = 8.9, 8.4 Hz, 1H), 5.711 (s, 1H), 6.075 (d, J = 5.7 Hz, 1H), 6.233 (d, J = 5.7 Hz, 1H), 6.915 (s, 1H), 7.129 (s, 1H), 8.95 (broad s, 1H).

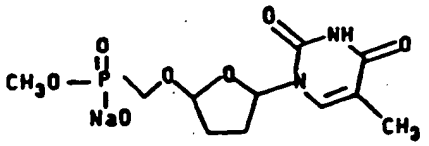
Example 27: 1-[2,3-Dideoxy-2,3-didehydro-4-beta-(methylphosphono)methoxy-beta-D-erthyrofuranosyl]-thymine sodium salt (27)



(27)

A solution of 1-[2,3-dideoxy-2,3-dihydro-4-beta-(dimethylphosphono)methoxy-beta-D-2-erthyrofuranosyl]thymine (180 mg, 0.54 mmol) in 1N-NaOH (2 mL) was stirred at 25° C for 2 hours. The reaction was carefully neutralized to pH 8.0 by dropwise addition of 1N-HCl with good stirring. Water was then evaporated in vacuo and the residue was purified by a C_{18} reverse phase column using water -3% acetonitrile as an eluent to give the title compound as a white solid: yield 125 mg (68%).
Analysis: Calcd. for $C_{11}H_{14}N_2O_7PNa$ 1.5 H_2O: C, 34.28; H, 4.93; N, 7.27.
Found: C, 34.02; H, 49.4; N, 7.19.
UV (H_2O): λ max 269 nm (ε = 8160)
^{1}H-NMR (300 MHz, D_2O): δ 1.847 (s, 3H), 3.525 (d, J = 11.0 Hz, 3H), 3.917 (dd, J = 13.6, 17.0 Hz, 1H), 3.765 (dd, J = 13.6, 17.0 Hz, 1H), 5.849 (s, 1H), 6.198 (d, J = 4.6 Hz, 1H), 6.415 (d, J = 4.6 Hz, 1H), 6.847 (s, 1H), 7.374 (s, 1H).

Example 28: 1-[2,3-Dideoxy-4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]thymine sodium salt (28)



(28)

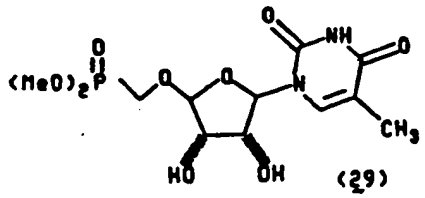
To a solution of 1-[2,3-dideoxy-2,3-didehydro-4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]thymine sodium salt (300 mg, 0.9 mmol) in water (20 mL) was added 10% palladium on active carbon (200 mg) and hydrogenated for 30 minutes under 35 psi H_2 pressure. The catalyst was filtered and washed with methanol (30 mL). The combined filtrate and wash was evaporated in vacuo and the residue was purified by a C_{18} reverse phase column using water -2% acetonitrile under 8 psi pressure to give the title compound as a white solid: yield 250 mg (84%).

This material showed an identical nmr with compound 21A which was prepared from 2,5-dimethoxytetrahydrofuran and the stereochemical assignment of compound 21A was confirmed by the NOE.

^{1}H-NMR (300 MHz, D_2O): δ 1.943 (s, 3H), 2.168 (m, 2H), 2.418 (m, 2H, 3.608 (d, J = 6.9 Hz, 3H), 3.68 (dd, J = 13.5, 18.0 Hz, 1H), 3.85 (dd, J = 13.5, 18.0 Hz), 5.303 (s, 1H), 6.390 (d, J = 6.3 Hz, 1H), 7.627 (s, 1H).

In a manner similar to the above Example 28, the thymine-containing reactant can be replaced with a corresponding adenine, guanine or cytosine reactant to produce 1-[2,3-dideoxy-2,3-didehydro-4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl] adenine sodium salt, or 1-[2,3-dideoxy-2,3-didehydro-4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl] guanine sodium salt, or 1-[2,3-dideoxy-2,3-didehydro-4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl cytosine sodium salt.

Example 29: 1-[4-beta-(Dimethylphosphono)methoxy-beta-D-erythrofuranosyl]thymine (29)



(29)

To a solution of 1-[2,3-dideoxy-2,3-didehydro-4-beta-(dimethylphosphono)methoxy-beta-D-erythrofuranosyl]thymine (3.31 g, 10 mmol) in pyridine (20 mL) was added osmium tetroxide (2.54g, 10mmol at 0 °C and stirred for 2 hours. hours. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate (100 mL), washed with 10% phosphoric acid (30 mL), water (20 mL), aqueous sodium bicarbonate (20 mL), brine and dried $MgSO_4$). The solvent was removed in vacuo, and the residual oil was chromatographed on silica gel using CH_2Cl_2-5% MeOH as an eluent to give the title compound as a white powder: yield 2.56 g (70%).

Analysis: Calcd. for $CH_{12}H_{19}N_2O_9P$: C, 39.35; H, 5.23; N, 7.65.

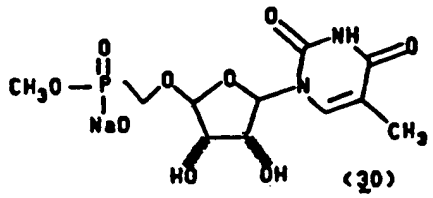
Found: C, 38.98; H, 5.09; N, 7.42.

^{13}C-NMR (75.47 MHZ, d_6-DMSO): δ 11.861, 52.672, 52.797, 59.114, 61.411, 72.608, 73.316, 73.399, 87.419, 107.607, 107.863, 110.810, 135.217, 150.973, 163.581.

^{1}H-NMR (300 MHz, d_6-DMSO): δ 1.675 (s, 3H), 3.540 (d, J = 10.5 Hz, 6H), 3.736 (1, J = 4.0 Hz, 1H), 3.817 (d, J = 9.6 Hz, 2H), 4.03 (dd, J = 6.0, 11.2 Hz, 1H), 4.763 (s, 1H), 5.35 (d, J = 4.0 Hz, 1H), 5.45 (d, J = 7.0 Hz, 1H), 5.919 (d, J = 6.9 Hz, 1H), 7.128 (s, 1H), 11.228 (broad s, 1H).

In a manner similar to the above Example 29, the thymine-containing reactant can be replaced with a corresponding adenine, guanine or cytosine reactant to produce 1-[4-beta-(dimethylphosphono)methoxy-beta-D-erythrofuranosyl]adenine, or 1-[4-beta-(dimethylphosphono) methoxy-beta-D-erythrofuranosyl]-guanine, or 1-[4-beta-(dimethylphosphono)methoxy-beta-D-erythrofuranosyl]cytosine.

Example 30: 1[4-(Methylphosphono)methoxy-beta-D-erythrofuranosyl]thymine Sodium Salt (30)



(30)

To a solution of 1-[4-beta-(dimethylphosphono)methoxy-beta-D-erythrofuranosyl]thymine (200 mg, 0.5 mmol) in 1N-NaOH (2 mL) was stirred at 25° C for 2 hours. The reaction was carefully neutralized to pH 9.0 by dropwise addition of 1N-HCl with stirring. Water was then evaporated in vacuo and the residual oil was purified by a C_{18} reverse phase column using water-2% acetonitrile as an eluent under 8 psi pressure to give the title compound as a white amorphous powder: yield 114 mg (56%).

Analysis Calcd. for $C_{11}H_{15}N_2O_9PNa\ 2H_2O$: C, 32.27; H, 4.64; N, 6.84.

Found: C, 31.94; H, 4.32; N, 6.86.

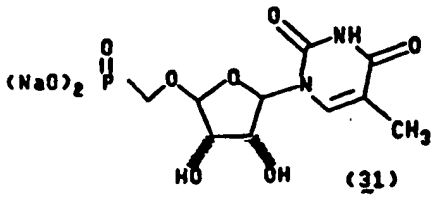
UV (H_2O): λ max 268 nm (ε = 8153).

^{13}C-NMR (75.47 MHz, D_2): δ 35.644, 35.719, 45.366, 47.479, 57.032, 57.411, 71.915, 92.426, 92.599, 96.463, 120.503, 137.007, 144.422, 151.377.

^{1}H-NMR (300 MHz, D_2O): δ 1.922 (s, 3H), 3.615 (D, J = 10.1 Hz, 3H), 3.687 (dd,J = 11.3, 11.1 Hz, 1h), 3.885 (dd, J = 11.3, 11.1 Hz, 1H), 4.220 (d, J = 4.3 Hz, 1H), 4.574 (dd, J = 6.7, 4.3 Hz, 1H), 5.09 (s, 1H), 6.175 (d, J = 6.7, Hz, 1H), 7.485 (s, 1H).

In a manner similar to the above Example 30, the thymine-containing reactant can be replaced with a corresponding adenine, guanine or cytosine reactant to produce 1-[4-beta-(methylphosphono)methoxy-beta-D- erythrofuranosyl]adenine, or 1-[4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]guanine, or 1-[4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]cytosine.

Example 31: 1-(4-beta-Phosphonomethoxy-beta-D-erythrofuranosyl)thymine disodium salt (31)



(31)

To a solution of 1-[4-beta-(diemthylphosphono)methoxy-beta-D-erythrofuranosyl]thymine (320 mg, 0.87 mmol) in DMF (2 mL) was added at 0° C bromotrimethylsilane (1.4 mL) under nitrogen. After stirring 90 minutes at 0° C, volatiles were removed in vacuo and the residue was neutralized to pH 8.0 by addition of aqueous saturated sodium bicarbonate. Water was then evaporated in vacuo and the residual solid was purified by a C_{18} reverse phase column using water-2% acetonitrile as an eluent to give the title compound as a white solid: yield 153 mg (46%). mp >250° C. (decomposition).

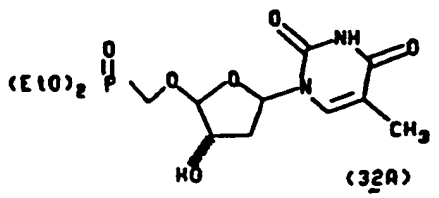
Analysis: Calcd. for $C_{10}H_{13}N_2O_9PNa\ 2H_2O$: C, 27.52; H, 4.35; N, 6.42.

Found: C, 27.05; H, 3.99; N, 6.12.

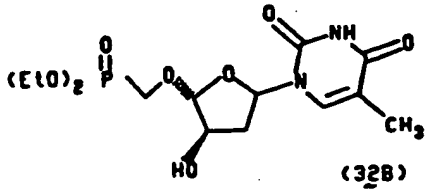
UV (H_2O): λ max 268 nm (ε = 7,568).
^{13}C-NMR (75.47 MHz, D_2O): δ 49.590, 51.582, 57.347, 57.541, 71.861, 93.034, 93.169, 95.541, 121.178, 136.393, 144.222, 150.601.
^{1}H-NMR (300 MHz, D_2O): δ 1.936 (s, 3H), 3.469 (dd, J = 12.3, 12.6 Hz, 1H), 3.756 (dd, J = 12.3, 12.6 Hz, 1H), 4.258 (d, J = 4.5 Hz, 1H), 4.578 (dd, J = 4.5, 6.2 Hz, 1H), 5.175 (s, 1h), 6.182 (d, J = 6.2 Hz, 1H), 7.591 (s, 1H).

In a manner similar to the above Example 31, the thymine-containing reactant can be replaced with a corresponding adenine, guanine or cytosine reactant to produce 1-[4-beta-phosphonomethoxy-beta-D-erythrofuranosyl]adenine disodium salt, or 1-[4-beta-phosphonomethoxy-beta-D-erythrofuranosyl]guanine disodium salt, or 1-[4-beta-phosphonomethoxy-beta-D-erythrofuranosyl]cytosine disodium salt.

Example 32: 1-[2-Deoxy-4-beta-(diethylphosphono)methoxy-beta-D-erythrofuranosyl]thymine (32A) and the trans isomer (32B).



(32A)



(32B)

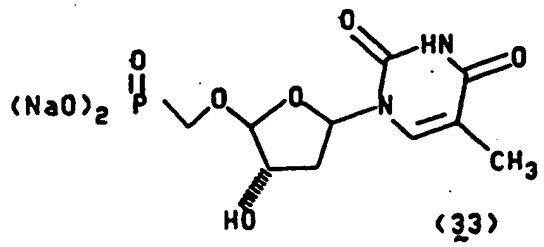
To a solution of 1-(2,3-dideoxy-3,4-didehydro-beta-D-erythrofuranosyl)thymine (2.4 g, 12.4 mmol) and diethylphosphonomethanol (17.4 g, 103 mmol) in CH_2Cl_2 (2 mL) was added 80-85% 3-chloroperoxybenzoic acid (17.4 g, 13.14 mmol) at 5° C. After stirring for 60 minutes at 25° C, the reaction mixture was purified by column chromatography on silica gel using CH_2Cl_2-3% MeOH to obtain the crude product, which was carefully rechromatographed on silica gel to separate the two isomers. Using CH_2Cl_2-1% MeOH, the minor isomer B was first eluted and obtained as a colorless oil: yield 75 mg (1.7%).
^{1}H-NMR (300 MHz, $CDCl_3$) of 32B: δ 1.287 (t, J = 6.9 Hz, 6H), 1.900 (s, 3H), 1.97-2.58 (m, 2H), 3.807 (dd, J = 9.0, 13.8 Hz), 4.016 (dd, J = 9.0, 13.8 Hz, 1H), 4.138 (m, 4H), 4.30 (m, 1H), 4.934 (d, J = 4.2 Hz, 1H), 6.321 (t, J = 6.6 Hz, 1H), 7.417 (s, 1H), 9.80 (broad s, 1H).

The silica gel column was continuously eluted with CH_2Cl_2-3% MeOH to obtain the major isomer 32A as a colorless oil: yield 735 mg (17%).
^{1}H-NMR (300 MHz, $CDCl_3$) of 32A: δ 1.310 (t, J = 7.5 Hz, 6H), 1.872 (s, 3H), 1.95 (m, 1H), 2.70 (m, 1H), 3.780 (dd, J = 9.3, 13.8 Hz, 1H), 3.928 (dd, J = 9.3, 13.8 Hz, 1H), 4.139 (m, 4H), 4.330 (d, J = 5.7 Hz, 1H), 5.268 (s, 1H), 6.238 (dd, J = 2.7, 8.4 Hz, 1H), 7.624 (s, 1H), 9.176 (broad s, 1H).

The stereochemical assignment of 32A and 32B was consistent with nmr NOE observation.

In a manner similar to the above Example 32, 1-(2,3-deoxy-3,4-didehydro-beta-D-erythrofuranosyl)-thymine can be replaced with a corresponding adenine, guanine or cytosine reactant to produce 1-[2-deoxy-4-beta-(diethylphosphono)methoxy-beta-D-erythrofuranosyl]adenine, 1-[2-deoxy-4-beta-(methylphosphono)-methoxy-beta-D-erythrofuranosyl]adenine sodium salt, or 1-[2-deoxy-4-beta-(diethylphosphono)methoxy-beta-D-erythrofuranosyl]guanine, or 1-[2-deoxy-4-beta-(diethylphosphono)methoxy-beta-D-erythrofuranosyl]-cytosine.

Example 33: 1-(2-Deoxy-4-beta-phosphonomethoxy-beta-D-erythrofuranosyl)thymine disodium salt (33)



(33)

To a solution of 1-[2-deoxy-4-(diethylphosphono)methoxy-beta-D-erythrofuranosyl]thymine (480 mg, 1.3 mmol) in DMF (2 mL) was added bromotrimethylsilane (2 mL) under nitrogen. After stirring 3 hours at 25° C, volatiles were removed in vacuo and the residue was carefully neutralized to pH 8.5 by addition of aqueous saturated sodium bicarbonate. Water was evaporated to dryness and the residual solid was purified by a C_{18} reverse phase column using water-3% acetonitrile as a eluent to give the title compound as a white powder: yield 165 mg (40%).

Analysis: Calcd. for $C_{10}H_{13}N_2O_8PNa_2\ 3H_2O$: C, 28.57; H, 4.52; N, 6.67.

Found: C, 28.48; H, 4.49; N, 6.52.

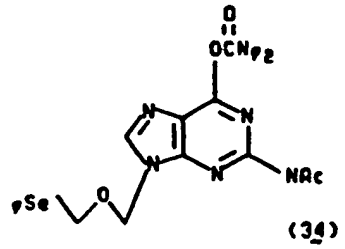
UV (H_2O): λmax 268 nm (ε = 7,602).

^{13}C-NMR (75.47 MHz, D_2O): δ 20.803, 48.289, 50.291, 56.714, 69.570, 94.015, 94.157, 94.994, 122.321, 135.750, 150.715.

^{1}H-NMR (300 MHZ, D_2O): δ 1.853 (s, 3H), 1.924 (dd, J = 2.6, 13.4 Hz, 1H), 2.8=785 (dd, J = 2.6, 5.3, 8.0 Hz, 1H), 3.415 (dd, J = 8.9, 12.4 Hz, 1H), 3.669 (dd, J = 8.9, 12.4 Hz, 1H), 4.372 (d, J = 5.3 Hz, 1H), 4.372 (d, J = 5.3 Hz, 1H), 4.372 (d, J = 5.3 Hz, 1H), 5.310 (s, 1H), 6.285 (dd, J = 2.6, 8.0 Hz, 1H), 7.776 (s, 1H).

In a manner similar to the above Example 33, the thymine-containing reactant can be replaced with a corresponding adenine, guanine or cytosine reactant to produce 1-(2-deoxy-4-beta-phosphonomethoxy-beta-D-erythrofuranosyl)adenine disodium salt, or 1-(2-deoxy-4-beta-phosponomethoxy-beta-D-erythrofuranosyl)-guanine disodium salt, or 1-(2-deoxy-4-beta-phosphonomethoxy-beta-D-erythrofuranosyl)-cytosine disodium salt.

Example 34: 2-Acetamino-6-diphenylcarbamoyloxy-9-[2-(phenylselenyl)ethoxymethyl]purine (34):



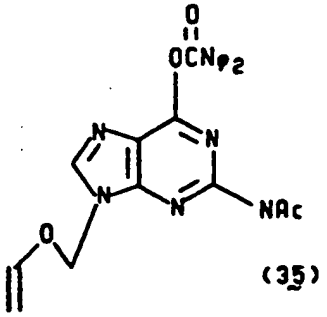
(34)

A mixture of 2-acetamino-6-diphenylcarbamoylpurine (36.7g, 94.6 mmol) [prepared according to the following literature procedure: R. Zou and M.J. Ropbins, Can. J. Chem., 65, No. 6, 1436 (1987)] and N,O-bis(trimethylsilyl)acetamide (47.6 mL, 193 mmol) in dry dichloroethane (700 mL) was heated at 80° C for 60 minutes. Volatiles were removed in vacuo and the residue was evaporated with toluene twice. The silylated purine and mercuric cyanide (29.6g, 117 mmol) in benzene (800 mL) was heated at reflux for 60 minutes, then a solution of 2-(phenylselenyl)ethoxymethyl chloride (24g, 94.5 mmol) in benzene (100 mL) was added dropwise. The mixture was refluxed for 4 hours and then allowed to stir for 15 hours at 25° C. The reaction was diluted with CH_2Cl_2 (500mL) and quenched with aqueous saturated bicarbonate (1L). The organic phase was washed with 2N potassium iodide (200 mL), dried ($MgSO_4$) and the solvents were removed in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2-5% MeOH as an eluent to provide the title compound as a slightly yellow powder: yield 22g (39%).

Analysis: Calcd. for $C_{25}H_{25}N_5O_4Se$: C, 57.91, H, 4.36; N, 13.98. Found: C, 57.76; H, 4.46; N, 13.48.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.459 (s, 3H), 2.951 (t,J = 6.9 Hz, 2H), 3.714 (t, J = 6.9 Hz, 2H), 5.477 (s, 2H), 7.07-7.7 (m, 15H), 8.001 (s, 1H), 8.171 (s, 1H).
^{13}C-NMR (75.45 MHz; $CDCl_3$): δ 25.133, 26.196, 69.192, 72.602, 120.363, 126.970, 127.014, 129.174, 141.686, 143.734, 150.247, 152.487, 155.232, 156.247, 156.297, 170.793.

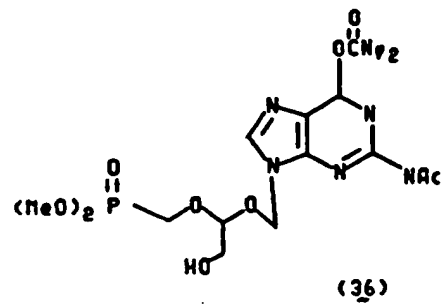
Example 35: 2-Acetamino-6-diphenylcarbamoyl-9-(vinyloxymethyl) purine (35):



(35)

To a solution of 2-acetamino-6-diphenylcarbamoyl-9-[2-(phenylselenyl)-ethoxymethyl]purine (4.92g, 8.16 mmol) in dioxane (80 mL) was added to 30% H_2O_2 (4 mL, 35 mmol) and sodium bicarbonate (2.1g, 24.5 mmol). The mixture was heated at 60° C for 20 minutes. The reaction was then concentrated to about 10mL, diluted with ethyl acetate (100 mL), dried ($MgSO_4$) and the solvents were removed in vacuo. The residue was dissolved in dioxane (40 mL), diisopropylethylamine (1.27g, 10 mmol) was added and the solution was heated at 80° C for 30 minutes under nitrogen. The solvent was evaporated in vacuo and the residual oil was chromatographed on silica gel using CH_2Cl_2-ethyl acetate (1:1) as an eluent to give the title compound as a yellowish powder: yield 2.3g (65%).
Analysis: Calcd. for $C_{23}H_{20}N_6O_4$ $0.5H_2O$: C, 60.98; H, 4.67; N, 18.55. Found: C, 61.20; H, 4.76; N, 18.84.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.485 (s, 3H), 4.170 (dd, J = 2.7, 6.6 Hz, 1H), 44.473 (dd, J = 2.7, 14.1 Hz, 1H), 6.395 (dd, J = 6.6, 14.1 Hz, 1H). 7.0-7.5 (m, 10H), 7.961 (s, 1H), 7.996 (s, 1H).
^{13}C-NMR (75.47 MHz, $CDCl_3$): δ 25.121, 70.572, 92.427, 126.272, 126.344, 126.443, 126.496,, 126.566, 126.644, 141.628, 143.226, 148.925, 152.552, 170.505.

Example 36: 2-Acetamino-6-diphenylcarbamoyloxy-9-[(2-hydroxy-1-(dimethylphonomethoxy)ethoxymethyl]-purine (36):

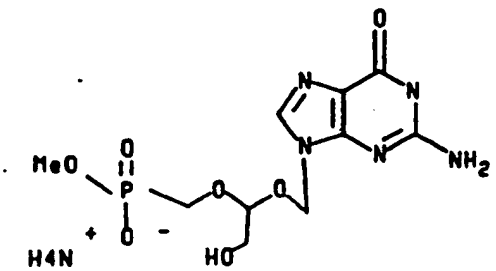


(36)

To a suspension of 2-acetamino-6-diphenylcarbamoyloxy-9-(vinyloxymethyl)purine (1.0g, 2.25 mmol) and dimethylphosphonomethanol (6 mL) in CH_2Cl_2 (6 mL) was added 80-85% m-chloroperbenzoic acid (611 mg, 3 mmol). After stirring for 18 hours at 25° C, the clear solution was diluted with CH_2Cl_2 (100 ml) and washed with ice cold 1N-NaOH (4 mL) and brine (20 mL). The organic phase was washed again with

brine (20 ML), dried ($MgSO_4$) and the solvent was removed in vacuo. The residual oil was chromatographed on silica gel using using CH_2Cl_2-5% MeOH as an eluent to give the title compound as a colorless oil: yield 360 mg (27%).
Analysis: Calcd. for $C_{26}H_{29}N_6O_9P$ $0.5CH_2Cl_2$: C, 49.22; H, 4.64; N, 13.00. Found: C, 49.89; H, 4.47; N, 12.76.
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.384 (s, 3H), 3.582 (dd, J = 4.5, 12.5 Hz, 1H), 3.722 (dd, J = 4.5, 12.5 Hz, 1H), 3.768 (dd, J = 2.9, 10.7 Hz, 6H), 3.798 (dd, J = 8.9, 14.0 Hz, 1H), 3.994 (dd, J = 8.9, 14.0 Hz, 1H), 4.910 (t, J = 4.9 Hz, 1H), 5.649 (d, J = 10.8 Hz, 1H), 5.723 (d, J = 10.8 Hz, 1H), 7.0-7.4 (m, 10H), 8.032 (s, 1H), 8.662 (s, 1H).

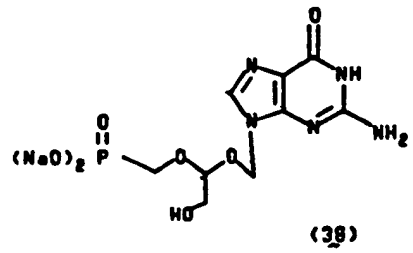
Example 37: 9[(2-Hydroxy-1-(methylphosphonomethoxy)ethoxymethyl]guanine ammonium salt (37):



(37)

A solution of 2-acetamino-6-diphenylcarbamoyloxy-9[(2-hydroxy-1-(dimethylphosphonomethoxy)ethoxy)-methyl]guanine (2.9g, 4.8 mmol) in methanol (300 mL) and 28% NH_4OH (300 mL) was heated at 60° C for 90 minutes. The solution was concentrated in vacuo and the residual oil was purified by C-18 reverse phase column chromatography using water as eluent under 8 psi pressure. The fractions having ultraviolet fractions were checked with HPLC, combined and lyophilized to give the title compound as a white powder: yield 1.15g (65%).
Analysis: Calcd. for $C_{10}H_{19}N_6O_7P$ H_2O: C, 31.26; H, 5.51; N, 21.87. Found: C, 31.63; H, 5.43; N, 21.72.
^{1}H-NMR (300 MHz, D_2O): δ 3.549 (d, J = 10.5 Hz, 3H), 3.571 (dd, J = 4.8, 13.2 Hz, 1H), 3.675 (dd, J = 9.3, 13.2 Hz, 1H), 3.4-3.6 (m, 2H), 4.844 (t, J = 3.9 Hz, 1H), 5.573 (d, J = 11.4 Hz, 1H), 5.638 (d, J = 11.4 Hz, 1H), 7.934 (s, 1H).
UV (H_2O): λ max 252 nm (ε = 13, 871).

Example 38: 9[(2-Hydroxy-1-(phosphonomethoxy)ethoxy)methyl]guanine disodium salt (38):

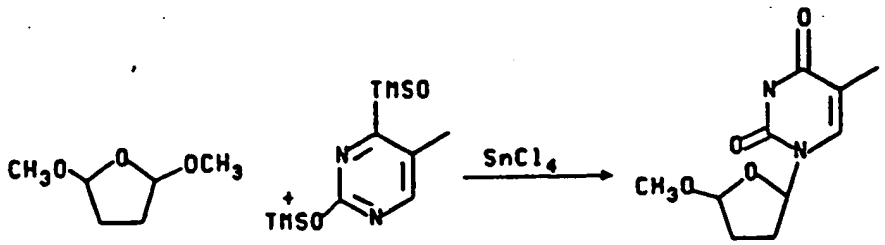


(38)

To a solution of 9-[2-hydroxy-1-(methylphosphonomethoxy)ethoxy)methyl]guanine ammonium salt (780 mg, 2.0 mmol) in dry DMF (20 mL) was added at 5° C bromotrimethysilllyl (8 mL, 60 mmol) under nitrogen. After stirring for 3 hours at 5° C, volatiles were removed in vacuo and the residue was dissolved in aqueous saturated bicarbonate and re-evaporated in vacuo to a solid. Purification of this material by C-18 reverse phase column chromatography using water as eluent under 8 psi pressure and lyophilization of combined

fractions gave the title compound as a white powder: yield 520 mg (62%).
Analysis: Calcd. for $C_9H_{12}N_5O_7PNa_2\ 2H_2O$: C, 26.04; H, 3.89; N, 16.87; Found: C, 26.25; H, 4.05; N, 16.89.
UV (H_2O): λ max 252nm (ϵ = 15,150).
^{1}H-NMR (300MHz, D_2O): δ 3.40-3.50 (m, 2H), 3.605 (dd, J = 5.4, 11.6 Hz, 1H), 3.698 (dd, J =9.0, 11.6 Hz, 1H), 4.877 (t, J = 4.5 Hz, 1H), 5.665 (d, J = 11.3 Hz, 1H), 5.725 (d, J = 11.3 Hz, 1H), 7.999 (s, 1H).
^{13}C-NMR (75.47 MHz, D_2O): δ 63.268, 65.832, 67.834, 71.636, 104.561, 104.712, 117.980, 141.823, 153.521, 156.320, 161.129.

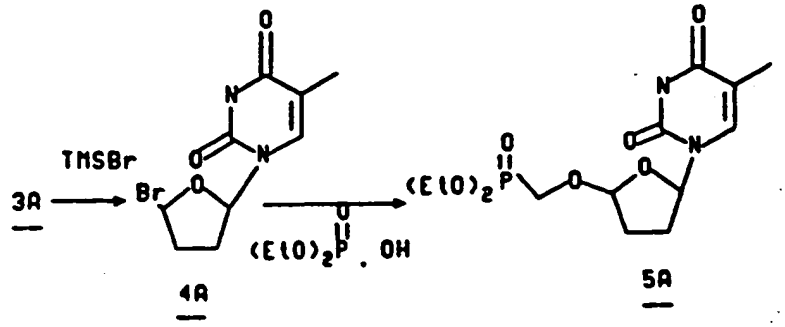
Example 39: 1-(4-Methoxytetrahydro-2-furyl)thymine (3A)



1A 2A 3A

To a suspension of 2.5 g (20 mmol) of dry, powdered thymine in 30 mL of hexamethyldisilazane was added 50 mg of ammonium sulfate and 0.5 mL of trimethylsilyl chloride. The mixture was heated at 140-145° (for 4 hours to obtain a clear solution). The excess hexamethyldisilazane was removed at reduced pressure, then the residual white oil was dissolved in xylene and evaporated in high vacuum to give a colorles viscous oil. The crude silyated thimine was dissolved in 40 mL of dichloroethane and cooled to -30°, followed by 7.8g (60 mmol) of 2.5 dimethoxytetrahydrofuran. To this solution was added 2.3 mL of tin tetrachoride via a syringe over 2 minutes, then stirred for 10 minutes under nitrogen. The mixture reaction was poured into ice-cold aqueous $NaHCO_3$ (100 mL)-ethylacetate (100 mL). The milky solution was filtered through celite and the organic Layer was separated and dried over $MgSO_4$. Evaporation of the dried solvents gave a yellow oil which was chromatographed on SiO_2 (CH_2CL_2-MeOH) to give 4.3 g (95%) of 3A as a colorless oil. This oil was a mixture of the two isomers (cis/trans) in a ratio of 1:1 as seen by analytical HPLC and ^{1}H-NMR.
^{1}H-NMR ($CDCl_3$) δ 1.4-2.2 (m, 7H), 3.40 and 3.42 (two s, 3H), 5.2 and 5.25 (two broad s, 1H), 6.20 and 6.41 (two q, 1H, J = 3.5, 7.0 Hz, and 4.0, 7.2 Hz), 7.02 and 7.40 (two s, 1H)

Example 40: 1-(5-Diethylphosphonomethoxytetrahydro-2-furyl)thymine (5A)



4A 5A

To a solution of 600 mg (2.65 mmol) of 3A (Example 39) in 15 mL of methylene chloride was added 0.6

mL of trimethylsilyl bromide and heated at 40-45°C for 10 minutes under nitrogen. The reaction was evaporated in vacuo to give 4AW as a yellow oil which was dissolved in 20 mL of methylne chloride followed by 440 mg (2.60 mmol) of diethylphosphonomethyl alcohol. This solution was cooled to -10°C followed by 0.6 ml of triethylamine and stirred for 15 minutes without the cooling bath. After dilution with 40 mL of ethylacetate, the reaction was washed with water and brine. Evaporation of the dried ($MgSO_4$) solvent gave a yellow oil which was chromtographed over SiO_2(CH_2CH_2-MeOH) to give 180mg (18.5%) of 5A as a white oil. This oil was a mixture of the two isomers cis/trans in a ratio of 1:1, as seen by analytical HPLC and ^1H NMR; ^1H-NMR($CDCl_3$) δ 1.25 (t, 6H, J = 7.0 Hz), 1.95 and 2.0 (two S, 3H), 3.8-4.0 (m, 2H),4.0-4.2 (m, 4H), 5.2 and 5.3 (two broad s, 1H), 6.2 and 6.42 (q,q, 1H, J =3.5, 7.0 Hz and 4.0, 7.2 Hz), 7.0 and 7.4 (two s, 1H).

Example 41: Testing and evaluation of compounds against herpes virus

A. Plaque Reduction Assay

Herpes simplex virus (HSV) strains were grown and titered at 37°C in vero cells (African Green Monkey Kidney cells) and used for virus work before the tenth passage.

Cells were grown and maintained in Earle's Minimum Essential Medium (EMEM), Gibco Laboratories, supplemented with 0.75% sodium bicarbonate, 2mM 1-glutamine, Pen-strep. and 5-10% fetal calf serum.

The titer of HSV strains is determined by a plaque titration method (Roizman and Roane, Virology, 115:75-79, 1961). Tissue culture 24-well petri dishes are seeded with cells and used for assays when approximately 75% monolayer. Volumes (0.1ml) of logarithmic dilutions of the virus strain are inoculated onto each of triplicate wells, and absorbed for one hour with intermittent shaking. The inoculum thereafter is removed, and 1 ml of 5-10% EMEM containing 0.3% human immune serum globulin is added. After a 48 hour incubation period at 37°C in a 5% CO_2 atmosphere, the overlay medium is removed and the cell sheets stained with Giemsa stain. The number of plaques is counted, the triplicate is averaged, and the number of plaque-forming units per ml is calculated.

The compounds are tested for activity against the herpes simplex stains using a stock solution of each compound freshly prepared. Appropriate dilution of each compound are made in 10% EMEM before usage. The antiviral efficacy of each compound is determined using the plaque reduction assay described above. Briefly, tissue culture 24-well plates, with approximately 50 plaque forming units of HSV per 0.1 ml, and the virus absorbed for 1 hour, with intermittent shaking. After removal of the inoculum, 1 ml of 10% EMEM containing two-fold dilutions of the appropriate drug are added in triplicates. Triplicate wells/plate receives no drug and are used as a virus control. After a 48-hour incubation period, at 37°C in a 5% CO_2 atmosphere, the overlay medium is removed, the cells are stained as described above, and plaques are counted. The counts of triplicate wells are averaged, and the number of plaques in the presence of each drug dilution are calculated.

The antiviral potency of the drug is determined by ID_{50}, the drug concentration necessary to reduce the number of plaques by 50% of those in the virus control cultures.

The results are shown in Table 1 herein below.

Table 1

Antiviral Test REsults of Compound 8 (see Example 8) against HSV-1 and HSV-2		
	ID_{50}(µg/ml)	
Compound	HSV-1	HSV-2
ACV (Acyclovir)	0.5	0.5
Compound 8	2.6	11

Example 42: Comparison of Compound 8 and Acyclovir (ACV) In Vivo

Groups of ten mice were inoculated intraperitoneally with from 200 to 600 PFU/0.2ml of Herpes simplex virus-1 (HL-34 strain). Different doses of test compound were administered to separate groups of animals on a BID basis for five consecutive days commencing three hours after inoculation. Treatment was by an intraperitoneal route. The experiment was teminated 21 days post inoculation and the number of survivals in each group was counted. The mean survival time (MST, days) was calculated.

The results are shown in Table 2. Compound 8 is equally as active as ACV.

Table 2

Antiviral Effect of Compound 8 Against HSV-1 Systemic Infection in Mice			
Compound	Dose (mg/kg/d)	Route	Survival
Compound 8	300	i.p.	10/10
	100	i.p.	9/10
	10	i.p.	3/10
ACV	200	i.p.	6/7
	100	i.p.	7/10

Treatment was initiated 3 hours post-infection and was given BID for 5 consecutive days.

Example 43: Testing andevaluating of compounds against Murine Retroviruses:

The compounds were evaluated for antiviral activity against murine leukemia virus (MuLV) strains using the UV-XC plaque assay (Rowe, et al., Virology, 42:1136, 1970).

The MuLV strains were grown in feral mouse cells (SC-1) and used for antiviral tests using the UV-XC plaque assay. Briefly, SC-1 cells are grown as monolayers in 4-well tissue culture plates and inoculated with approximately 50-100 plaque forming units of MuLV in 0.5 ml of 5% EMEM containing 20 µg/ml DEAE/Dextran. After 1 hour adsorbtion, the inoculum is removed and 5 ml of 5% EMEM containing three-fold dilutions of the appropriate drug are added. Five days later, the cultures are UV-irradiated with an ultraviolet lamp and rat XC sarcoma cells are added to the cultures. Three-four days after UV-irradiation, the cell cultures are stained with Giemsa stain and the plaques are enumerated. Antiviral activity is expressed in terms of the reduction in the mean number of UX-XC plaques counted in the drug treated, virus-infected cultures compared with mean number of plaques counted in untreated, virus-infected control cultures.

Example 44: In Vitro Evaluation Against HIV.

The HIV in vitro assay described as follows was used: The anti-HIV/LAV activity is measured in cultures of CEM-F cells. The GEM cells are infected with approximately 30 $TCID_{50}$ (50% tissue culture infectious dose of HIV (LAV strain). The cells are then incubated for 45 minutes at 37°C. The test compounds in culture medium are added at various concentrations to the infected cells and then incubated for a further 8 days. After 8 days the antiviral activity was evaluated in the culture media supernatant for p-24 gag protein by an enzyme capture assay (ELISA). The antiviral activity was expressed as the dose that inhibits 50% of the virus expression (ID_{50} in µg/mL) as detected by the assay described.

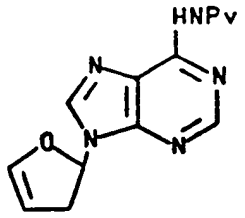
Table 3

Antiviral Test Results of Compound 25 (see Example 25) against Retroviruses		
	ID_{50}(μg/mL)	
Compound	R-MuLV	HIV
AZT	0.05	0.1
Compound 25	0.3	1.8

It will be appreciated that the instant specification and claims are set forth by way of illustration and not limitation and that various modifications and changes may be made without departing form the spirit and scope of the present invention.

Example 45

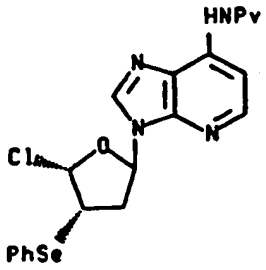
6-N-Pivaloyl-9-(2,3-dideoxy-3,4-dihydro-β-D-erythrofuranosyl)-adenine



To a solution of 9-(2,3-dideoxy-3,4-dihydro-β-D-erythrofuranosyl)adenine (2.0 g, 10 mmol) [prepared according to the literature procedure: J. Zemlicka, R. Gasser, J. V. Freisler, J. P. Norwitz, J. Amer. Chem. Soc., 94, 3213 (1972)] in 1,2-dichloroethane (10 mL) was added pyridine (1 mL), dimethylaminopyridine (170 mg) and pivaloyl chloride (1.5 g, 12 mmol). The resulting solution was heated at 55-60 °C for 6 h under nitrogen. The mixture was then concentrated in vacuo, taken up in CH_2Cl_2 and washed with water, 20% H_3PO_4 and brine, dried over $MgSO_4$, and evaporated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2-3% MeOH as eluent to give 2 (2.45 g, 85%) as a white powder.
^1H NMR ($CDCl_3$) δ 1.24 (s, 9H), 2.29 (ddd, J = 3.5, 5.0, 17.1 Hz, 1H), 3.33 (dddd, J = 2.4, 5.0, 9.4, 17.1 Hz, 1H), 5.24 (dd, J = 2.4, 5.0 Hz, 1H), 6.41 (dd, J = 3.5, 9.4 Hz, 1H), 6.48 (dd, J = 2.4, 5.0 Hz, 1H), 8.18 (s, 1H), 8.73 (s, 1H).

Example 46

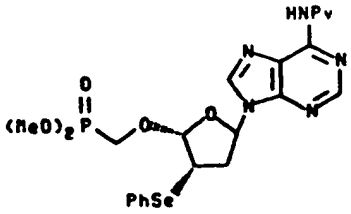
6-N-Pivaloyl-9-[2,3-dideoxy-4-β-chloro-3-α-(phenylselenyl)-β-D-erythrofuranosyl]adenine



To a solution of the product of Example 45 (3.5 g, 12.2 mmol) in CH_2Cl_2 (40 mL) was added at -25° C a solution of phenylselenyl chloride (2.7 g, 14.0 mmol) in CH_2Cl_2 (7 mL) over 5 min under nitrogen. After stirring for 30 min at -25° C, the solvent was removed in vacuo to give 3 as a yellow oil. This material was used promptly for the next reaction:
^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.88 (m, 1H), 3.23 (m, 1H), 4.36 (d, J = 6.3 Hz, 1H), 6.29 (s, 1H), 6.80 (dd, J = 6.6, 8.4 Hz, 1H), 8.53 (s, 1H), 8.77 (s, 1H).

Example 47

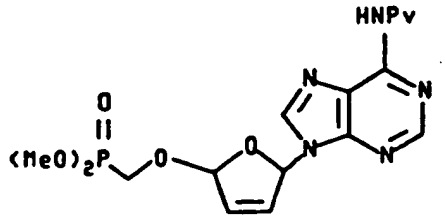
6-N-Pivaloyl-9-[2,3-dideoxy-4-β-dimethylphosphono)methoxy-3-α-(phenylselenyl)-β-D-erythrofuranosyl]-adenine



To a solution of the product of Example 46 (approximately 12 mmol) and dimethyl hydroxymethylphosphonate (16.8 g, 120 mmol) [prepared according to the literature procedure: D.P. Philion and S.S. Andres, Tetrahedron Lett. 27, 1477 (1986)] in CH_2Cl_2 (15 mL) was added at -25° C a suspended solution of silver perchlorate (4.0 g, 20 mmol) in CH_2Cl_2 (10 mL) and dimethyl hydroxymethylphosphonate (5 mL) over 5 min under nitrogen. The mixture was allowed to warm to 0° C, stirred for 60 min and was then poured into CH_2Cl_2 (100 mL)-aqueous bicarbonate (100 mL)-brine (50 mL). The organic phase was separated after filtration, fried over $MgSO_4$ and evaporated. The residual oil was chromatographed on silica gel using CH_2Cl_2-5% MeOH as eluent to give 4 (3.2 g, 45%) as a colorless oil:
^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H), 2.61 (ddd, J = 2.7, 6.6, 14.4 Hz, 1H), 2.96 (ddd, J = 6.6, 7.5, 14.4 Hz, 1H), 3.68 (d, J = 11 Hz, 6H), 3.7-4.0 (m, 3H), 5.24 (s, 1H), 8.27 (s, 1H), 8.67 (s, 1H).

Example 48

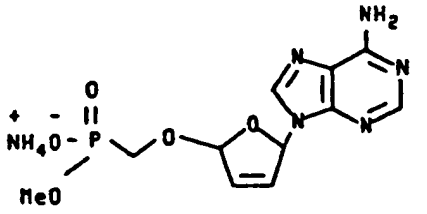
6-N-Pivaloyl-9-[2,3-dideoxy-2,3-dihydro-4-β-(dimethylphosphono-methoxy-β-D-erythrofuranosyl]adenine



To a solution of the product of Example 47 (3.3 g, 5.6 mmol) in dioxane (30 mL) was added a solution of sodium periodate (6.3 g, 30 mmol) in water (30 mL) and the resulting solution was stirred at 23° C for 4 h. CH_2Cl_2 (200 mL)was added and the mixture was filtered through celite. The organic phase was washed with water, brine, dried over $MgSO_4$ and evaporated in vacuo. The residual oil was chromatographed on silica gel using CH_2CL_2-5% MeOH as eluent to give 5 (1.4 g, 57%) as a colorless oil:
^1H NMR ($CDCl_3$) δ 1.31 (s, 6H), 3.64 (d, J = 10.8 Hz, 3H), 3.71 (d, J = 10.8 Hz, 3H), 3.84 (dd, J = 8.7, 9.9 Hz, 1H), 5.87 (s, 1H), 6.27 (d, J = 6.0 Hz, 1H), 6.34 (dd, J = 1.5, 6.0 Hz, 1H), 7.00 (d, 3 = 1.5 Hz, 1H), 8.04 (s, 1H), 8.66 (s, 1H);
^{13}C NMR ($CDCl_3$) δ 27.524, 40.607, 53.318 (d, J = 6.2 Hz), 61.598 (d, J-165 Hz), 86.247, 109.202, 123.406, 130.657, 132.679, 141.966, 150.205, 152.056, 176,547.

Example 49

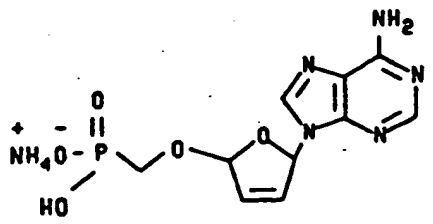
9-[2,3-Dideoxy-2,3-didehydro-4-β-(methylphosphono)methoxy-β-D-erythrofuranosyl]adenine sodium salt.



A solution of the product of Example 48 (330 mg, 0.78 mmol) and sodium methoxide (250 mg, 4.6 mmol) in methanol (10 mL) was stirred at 23° C for 18 h. The reaction was carefully neutralized to pH 5.0 by dropwise addition of 2N-HCl in an ice bath. The pH of the solution was readjusted to 8.0 by concentrated NH_4OH and volatiles were removed in vacuo. The solid residue was purified by C_{18} reverse-phase column using water as eluent under 8 psi pressure to give 6 (141 mg, 49%) as a white amorphous powder:
^1H NMR (D_2O) δ 3.34 (d, J = 10.5 Hz, 3H), 3.65 (dd, J = 9.2, 13.2 Hz, 1H), 3.80 (dd, J = 9.2, 13.2 Hz, 1H), 5.99 (s, 1H), 6.57 (s, 2H), 6.83 (s, 1H), 8.11 (s, 1H), 8.14 (s, 1H);
^{13}C NMR (D_2O) 58.542 (d, J = 3.0 Hz), 68.483 (d, J-150 Hz), 92.797, 116.319, 125.121, 136.147, 139.719, 147.131, 155.275, 159.781, 162.359;
UV max (H_2O) 260 nm (ε 12,964).
Anal. Calcd for $CH11^H13^N5^O5$ PNa H_2O: C, 35.97; H, 3.90; N, 1907.
Found: C, 35.53; H, 3.71; N, 18.78.

Example 50

9-[2,3-Dideoxy-2,3-dihydro-4-β-phosphonomethoxy-β-D-erythrofuranosyl]adenine ammonium salt



A solution of the product of Example 49 (310 mg, 0.9 mmol) and trimethylsilylbromide (1.0 mL) in DMF (4 mL) was stirred at 0 °C for 3 h under nitrogen. Volatiles were removed in vacuo and the residue was dissolved in concentrated NH_4OH (2 mL). Water was evaporated in vacuo and the residual solid was purified by C_{18} reverse-phase column using water as eluent under 8 psi pressure to give 7 (128 mg, 43%) as a white amorphous powder.

UV max (H_2O) 260 nm (ε 14,982);

^1H NMR (D_2O) δ 3.59 (dd, J = 9.3, 22.2 Hz, 1H), 3.69 (dd, J = 9.3, 22.2 Hz, 1H), 5.99 (s, 1H), 6.46 (d, J = 6.0 Hz, 1H), 6.50 (d, J = 6.0 Hz, 1H), 6.83 (s, 1H), 7.87 (s, 1H), 8.13 (s, 1H);

^{13}C NMR (D_2O) δ 70.756 (d, J-150 Hz), 93.065, 116.510, 122.434, 136.579, 139.835, 147.763, 155.424, 158.990, 161.809.

Anal. Calcd for $C_{10}H_{15}N_6O_5P\ 3H_2O$: C, 31.25; H, 5.46; N, 21.87.

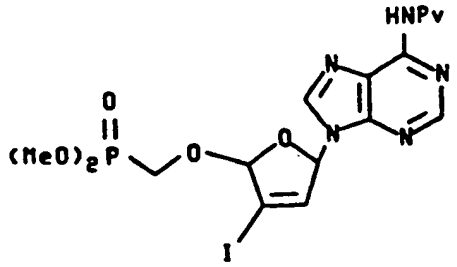
Found: C, 31.32; H, 5.85; N, 22.15.

This compound was evaluated for anti-retroviral activity by the methods described in Examples 43 and 44. The following results were obtained. AZT controls were run simultaneously to confirm the validity of the test.

Virus	Cell-line	Cell-tox.	ID_{50}
HIV	CEM	>100um	45um
MuLV	SC-1	>100um	<0,1um
HIV	MT-4	>500um	1.5um
MuLV-R	SC-1	>100um	0.01um

Example 51

6-N-Pivaloyl-9-[2,3-dideoxy-4-β-(dimethylphosphono)methoxy-3-α-iodo-β-D-erythrofuranosyl]adenine

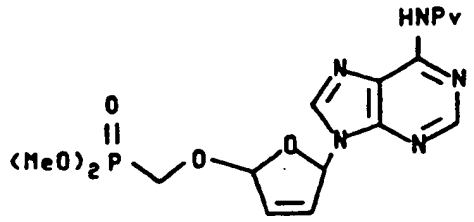


To a solutin of the product of Example 45 (3.5 g, 12.2 mmol) and dimethyl hydroxymethylphosphonate (16.8 g, 120 mmol) in CH_2Cl_2 (40 mL) was added portionwise at 0 °C N-iodosuccinimide (2.75 g, 12.2 mmol) and the mixture was stirred for 2 h at 0 °C. The reaction was diluted with CH_2Cl_2 (50 mL), washed with water, brine, and dried over $MgSO_4$. The residual oil was chromatographed on silica gel using CH_2Cl_2-3% MeOH as eluent to give 8 (4.9 g, 72%) as a slightly yellow oil.

^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 2.89 (dd, J=6.3, 9.7 Hz, 1H), 3.20 (dd, J-6.3, 10.3 Hz, 1H), 3.7-3.9 (m, 8H), 4.49 (d, J-5.4 Hz, 1H), 5.50 (s, 1H), 6.86 (t, J=7.2 Hz, 1HH), 8.29 (s, 1H), 8.50 (broad s, 1H), 8.74 (s, 1H).

Example 52

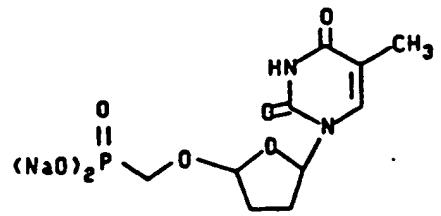
6-N-Pivaloyl-9-[2,3-dideoxy-2-3-dihydro-4-β-(dimethylphosphono)methoxy-β-D-erythrofuranosyl]adenine



A solution of the product of Example 51 (1.7 g, 3.0 mmol) and 1,8-diazabicyclo [5,4,0] under-7-ene (912 mg, 6.0 mmol) in $CHCl_3$ (20 mL) was heated at 65°C for 2 h. The reaction was washed with ice-cold 20% N_3PO_4, brine, dried over $MgSO_4$ and evaporated in vacuo. The residual oil was purified on silica gel using CH_2Cl_2-3% MeOH to give 5 (1.2 g, 90%) as a colorless oil. This material was identical with the product of Example 48.

Example 53

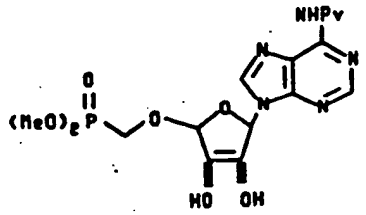
1-[2,3-Dideoxy-4-β-(phosphonomethoxy)-β-D-erythrofuranosyl]thymine disodium salt



A mixture of the product of Example 25 (200 mg, 0.57 mmol) and 10% palladium on active carbon (180 mg) in water (20 mL) was hydrogenated for 30 min. under 30 psi H_2 pressure in the Parr hydrogenator. The catalyst was filtered through celite with the aid of a water wash. Water was removed by lyophilization to give the desired product (205 mg), 100%) as a white amorphous powder:
UV max (H_2O) 268 nm (ε 8844);
^{1}H NMR (D_2O) δ 1.86 (s, 3H), 2.0-2.4 (m, 4H), 3.41 (dd, J=8.1, 12.9 Hz, 1H), 3.62 (dd, J=8.1, 12.9Hz, 1H), 5.32 (t, J-2.7Hz, 1H), 6.24 (t, J=7.0 Hz, 1H), 7.60 (s, 1H);
^{13}C NMR (D_2O) δ 18.496, 35.384, 38.041, 72.628, (d, J=150 H_3), 93.249, 113.423, 118.884, 159.494, 174.169,
Anal. Calcd. for $C_{10}H_{13}N_2O_7$ PNa_2 1 1/2 H_2O: C, 31.83; H, 4.24; N, 7.42.
Found: C, 31.62; H, 3.95; N, 7.28

Example 54

6-N-Pivaloyl-9-[4-β-(dimethylphosphono)methoxy-β-D-erythrofuranosyl]adenine

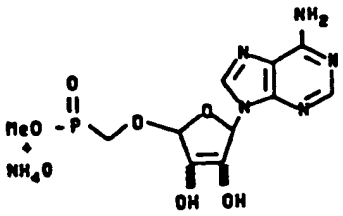


To a solution of phenylboric acid (860 mg, 7.0 mmol) and 4-methylmorpholine N-oxide (900 mg, 7.5 mmol) in CH_2Cl_2 (20 mL) was added at 23° C osmium tetroxide (25 mg) followed by the product of Example 52 (2.75 g, 6.4 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 2h and 10% aqueous sodium bisulfite (4 mL) was added. After stirring for 1h, the CH_2Cl_2 was separated, washed with brine and dried over $MgSO_4$. Evaporation of solvent gave a white oil which was dissolved in acetone (15 mL) and 1,3-dipropanol (760 mg, 10 mmol). All volatiles were removed in vacuo and the resulting oil was chromatographed over silica gel using the above named compound CH_2Cl_2-7% MeOH as eluent to give (2.3 g, 76%) as a white foam:

^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 3.72 (d, J = 10.5Hz, 6H), 3.73 (dd, J = 10.6, 13.5Hz, 1H), 3.95 (d, J = 10.6, 13.5 Hz, 1H) 4.91 (dd,J = 4.5, 6.3 Hz, 1H), 4.33 (d, J = 4.5 Hz, 1H), 5.09 (s, 1H), 6.38 (d, J = 6.3Hz, 1H), 8.35 (s, 1H), 8.49 (s, 1H), 8.83 (broad s, 1H).

Example 55

9-[4-β-(Methoxyhydroxyphosphinyl)methoxy-β-D-erythrofuranosyl]adenine ammonium salt



A solution of the product of Example 54 (2.2g, 4.8 mmol) and sodium methoxide (1.49, 26 mmol) in methanol (50 mL) was stirred at 23° C for 7 h under nitrogen. Volatiles were removed in vacuo and the residual oil was dissolved in water (20 mL). The aqueous solution was heated at 35.o℃ for 10 h. The reaction was carefully neutralized to pH 5.0 by dropwise addition of 2N-HCl in an ice bath. The solution was then readjusted to 8.0 with concentrated NH_4OH and volatiles were removed in vacuo. The solid residue was purified by C_{18} reverse-phase column using water -5% CH_3Cl as eluent under 8 psi pressure to give 11 (1.3g, 75%):

UV max (H_2O) 260 nm (ε 10,019);

^{1}H NMR (D_2O) 3.56 (d, J-10.5 Hz, 3H), 3.61 (dd, J = 10, 12.9 Hz, 1H), 3.83 (dd, J = 10, 12.9 Hz, 1H), 4.38 (d, J-11.0 Hz, 1H), 5.0 (dd, J-6.2, 11.0 Hz, 1H), 5.19 (s, 1H);

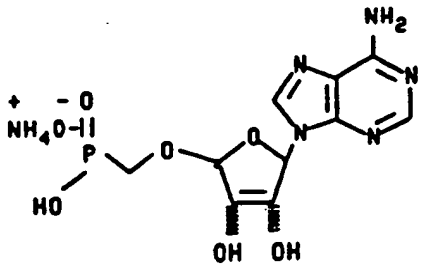
^{13}C NMR (D_2O) δ 53.897 (d, J-6.0 Hz), 64.192 (d, J-150 Hz), 75.589, 75,909, 111.096, 141,824, 151.079, 154,785, 157.354.

Anal. Calc. for $CH_{11}H_{14}N_5O_7$ p. 1 3/4 NaCl: C, 28.46; H, 3.47; N, 15.08.

Found: C, 28.59; H, 3.43; N, 14.72.

Example 56

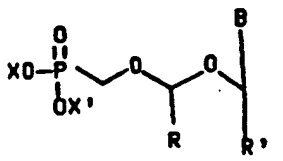
9-[4-β-(phosphonomethoxy)methoxy-β-D-erythrofuranosyl]adenine ammonium salt



A solution of the product of Example 55 (1.5 g, 4.1 mmol) and trimethylsilyl bromide (7 mL) in DMF (30 mL) was stirred at 23.o°C for 6 h under nitrogen. The volatiles were removed in vacuo and the residue was dissolved in concentrated NH_4OH (3 mL). Water was evaporated in vacuo and the residual solid was purified by C_{18} reverse-phase column using water as eluent to give 12 (600 mg, 40%) as a white amorphous powder:
UV max (H_2O) 262 nm (ε 12,640);
^1H NMR (D_2O) δ 3.56 (dd, J = 10.0, 12.9 Hz, 1H), 3.79 (dd, J = 10.0, 12.9Hz, 1H), 4.31 (d, J = 11.0 Hz, 1H), 4.92 (dd, J = 6.0, 11.0 Hz, 1H), 5.17 (s, 1H), 6.08 (d, J = OHz, 1H), 8.24 (s, 1H), 8.25 (s, 1H).
^{13}C NMR (D_2O) δ 66.296 (d, J = 157 Hz), 75.881, 76.967, 88.982, 111.148, 119.927, 142.208, 150.689, 153.560, 156.330.
Anal. Calcd. for $C_{10}H_{17}N_5O_7$ P H_2O: C, 30.05; H, 5.26, N. 21.03.
Found: C, 30.09; H, 5.06; N, 20.38

Claims

1. A phosphonomethoxymethoxymethyl purine or pyrimidine derivative of the formula



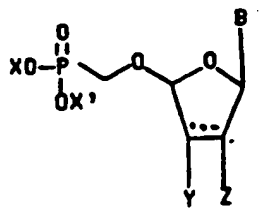
wherein X and X′ are the same or different and are hydrogen, alkyl having 1 to 6 carbon atoms, or the cation of a salt-forming base,
R and R′ are the same or different and are hydrogen, alkyl with 1 to 6 carbon atoms, hydroxyalkyl with 1 to 6 carbon atoms or alkanoyl having 2 to 7 carbon atoms,
B is a purine or pyrimidine base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted guanine, purine, substituted purine, cytosine, substituted cytosine, thymine, uracil, substituted uracil, adenine and substituted adenine,
and pharmaceutically acceptable salts thereof.

2. A phosphonomethoxymethoxymethyl purine or pyrimidine derivative according to claim 1, wherein X and X′ are the same or different and are H, ethyl, methyl, or Na, and
R and R′ are the same or different and are H or CH_3.

3. A phosphonomethoxymethoxymethyl purine or pyrimidine derivative according to claim 1, wherein said derivative is selected from the group consisting of (a) 9-[(phosphonomethoxy) methoxymethyl]guanine disodium salt, (b) 1-[(phosphonomethoxy) methoxymethyl]cytosine disodium salt, (c) 9-[-(phosphonomethoxy)methoxymethyl] adenine disodium salt, (d) 9-[1(phosphonomethoxy)ethoxy methyl] guanine disodium salt, (e)9-[(2-hydroxy-1-phosphonomethoxyethoxy)methyl]guanine disodium salt, (f) 9-[(2-hydroxy-1-phosphonomethoxyethoxy)methyl]adenine disodium salt, (g) 9-[(2-hydroxy-1-phosphonomethox-

yethoxy methyl] cytosine disodium salt and (h) 9-[(2-hydroxy-1-phosphonomethoxyethoxy)methyl]thymine disodium salt.

4. A dihydro-2-furyl or tetrahydro-2-furyl-1-substituted pyrimidine or 9-substituted purine derivative of the formula



wherein the broken line refers to an optional double bond, X and X' are the same or different and are H, alkyl with 1 to 6 carbon atoms, or the cation of a salt-forming base,
Y and Z are the same or different and are H, OH, unsubstituted or substituted alkyl having 1 to 6 carbon atoms, and
Y and Z together are an oxygen atom or a methylene group in which event the broken line is a single bond
B is a 9-substituted purine or 1-substituted pyrimidine base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted substitued guanine, purine, substituted purine, cytosine, substituted cytosine, thymine, uracil, substituted uracil, adenine and substituted adenine,
and pharmaceutically acceptable salts thereof.

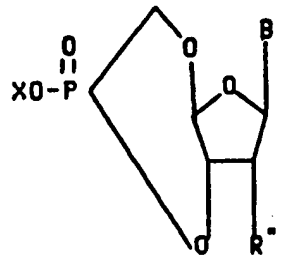
5. A purine or pyrimidine derivative according to claim 4, wherein Y and Z are the same or different and are alkyl having 1 to 6 carbon atoms substituted by a substituent selected from the group consisting of halogen, hydroxy, amino, or azido.

6. A purine or pyrimidine derivative according to claim 4, wherein said derivative is selected from the group consisting of

(a) 1-(4-phosphonomethoxytetrahydro-2-furyl)thymine disodium salt,
(b) 1-[2,3-dideoxy-2,3-didehydro-4-phosphonomethoxy-beta-D-erythrofuranosyl]thymine disodium salt,
(c) 1-[2,3-dideoxy-2,3-didehydro-4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]thymine sodium salt,
(d) 1-[2,3-dideoxy-4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]thymine sodium salt,
(e) 1-[2,3-dideoxy-2,3-didehydro-4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]adenine sodium salt,
(f) 1-[2,3-dideoxy-2,3-didehydro-4-beta-methylphosphono)methoxy-beta-D-erythrofuranosyl]guanine sodium salt,
(g) 1-[2,3-dideoxy-2,3-didehydro-4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]cytosine sodium salt,
(h) 1-[4-beta-(dimethylphosphono)methoxy-beta-D-erythrofuranosyl]thymine,
(i) 1-[4-beta-(dimethylphosphono)methoxy-beta-D-erythrofuranosyl]adenine.
(j) 1-[4-beta-(dimethylphosphono)methoxy-beta-D-erythrofuranosyl]guanine.
(k) 1-[4-beta-(dimethylphosphono)methoxy-beta-D-erythrofuranosyl]cytosine,
(l) 1-[4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]thymine,
(m) 1-[4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]adenine,
(n) 1-[4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl]guanine,
(o) 1-[4-beta-methylphosphono)methoxy-beta-D-erythrofuranosyl]cytosine,
(p) 1-[4-beta-phosphonomethoxy-beta-D-erythrofuranosyl)thymine disodium salt,
(q) 1-[4-beta-phosphonomethoxy-beta-D-erythrofuranosyl)adenine disodium salt,
(r) 1-[4-beta-phosphonomethoxy-beta-D-erythrofuranosyl)cytosine disodium salt,
(s) 1-[4-beta-phosphonomethoxy-D-erythrofuranosyl)-cytosine disodium salt,
(t) 1-[2-deoxy-4-beta (diethylphosphano)methoxy-beta-D-erythrofuranosyl Jthymine,
(u) 1-[2-deoxy4-beta-(diethylphosphono)methoxy-beta-D-erythrofuranosyl]adenine.
(v) 1-[2-deoxy-4-beta-(diethylphosphono)methoxy-beta-D-erythrofuranosyl]guanine,
(w) 1-[2-deoxy-4-beta-(diethylphosphono)methoxy-beta-D-erythrofuranosyl]cytosine,
(x) 1-(2-deoxy-4-beta-phosphonomethoxy-beta-D-erythrofuranosyl)thymine disodium salt,
(y) 1-(2-deoxy-4-beta-phosphonomethoxy-beta-D-erythrofuranosyl)adenine monoammonium salt,
(z) 1-(2-deoxy-4-beta-phosphonomethoxy-beta-D-erythrofuranosyl guanine disodium salt,

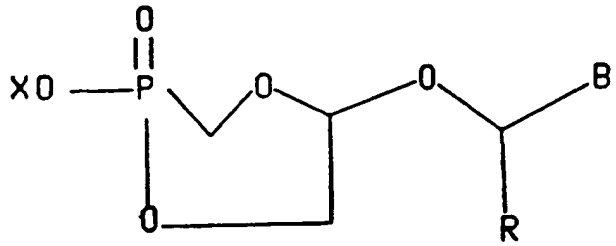
(aa) 1-(2-deoxy4-beta-phosphonomethoxy-beta-D-erythrofuranosyl)cytosine disodium salt, and
(ab) 1-(2-deoxy-4-beta-(methylphosphono)methoxy-beta-D-erythrofuranosyl)adenine sodium salt.

7. A purine or pyrimidine derivative of the formula



wherein X is H, alkyl with 1 to 6 carbon atoms, R" is H or OH and B is a base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted guanine, purine, substituted purine, cytosine, substituted cytosine, uracil, substituted uracil, thymine, adenine and substituted adenine, and pharmaceutically acceptable salts thereof.

8. A phosphonomethoxymethyoxymethyl purine/pyrimidine derivative having a cyclic phosphonate group of the formula



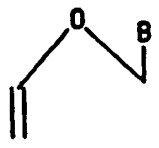
wherein X is H, alkyl with 1 to 6 carbon atoms, R is H, alkyl with 1 to 6 carbon atoms, hydroxyalkyl with 1 to 6 carbon atoms, or R"CO-wherein R" is an alkyl with 1 to 6 carbon atoms, and B is a purine or pyrimidine base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted cytosine, uracil, substituted uracil, thymine, adenine and substituted adenine, and pharmaceutically acceptable salts thereof.

9. A pharmaceutical composition comprising as an active ingredient an anti-viral or anti-retroviral or anti-neoplastic amount of at least one compound according to any one of claims 1 to 8 in admixture with a solid, liquid or gaseous diluent.

10. The use of at least one compound according to any one of claims 1 to 8 for preparing a pharmaceutical composition for treating an infection with a virus or retrovirus or for treating a tumor.

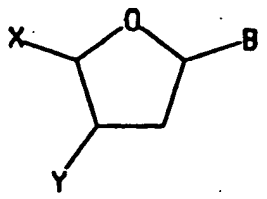
11. An oligonucleotide derived from a 4'-phosphonomethoxytetrahydrofuranyl-1'-purine/pyrimidine derivative according to claim 4.

12. A compound of the formula



wherein B is a purine or pyrimidine base selected from the group consisting of xantine, substituted xanthine, guanine, substituted guanine, purine, substituted purine, cytosine, substituted cytosine, thymine, uracil, substituted uracil, adenine and substituted adenine.

13. A compound of the formula

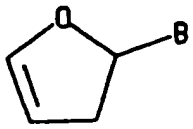


wherein X is a halogen, Y is



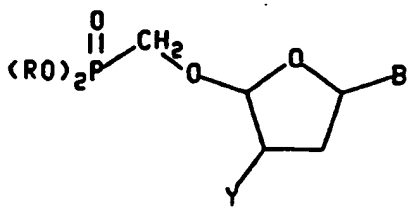
or a halogen and B is a purine or pyrimidine base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted guanine, purine, substituted purine, cytosine, substituted cytosine, thymine, uracil, substituted uracil, adenine and substituted adenine.

14. A compound of the formula

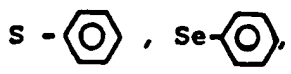


wherein B is a purine or pyrimidine base selected from the group consiting of guanine, substituted guanine, cytosine, and substituted cytosine.

15. A compound of the formula

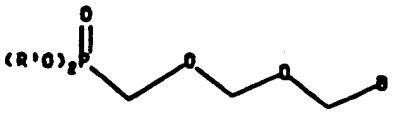


wherein Y is a halogen,

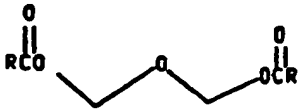


R is hydrogen or alkyl with 1 to 6 carbon atoms and B is a purine or pyrimidine base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted guanine, purine, substituted purine, cytosine, substituted cytosine, thymine, uracil, substituted uracil, adenine and substituted adenine.

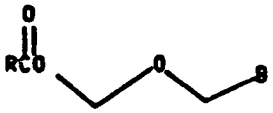
16. A process for preparing a compound of the formula



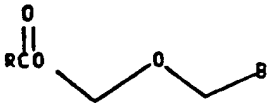
comprising reacting a compound of the formula



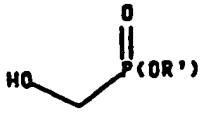
with a silylated purine or a silylated pyrimidine in the presence of a Lewis acid to form a compound of the formula



and reacting said

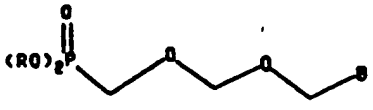


with a compound of the formula

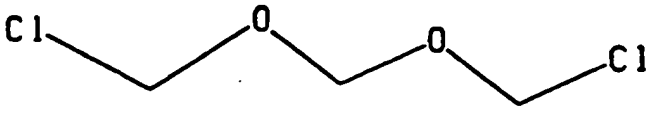


in the presence of a Lewis acid, wherein R is an alkyl having 1 to 6 carbon atoms or an unsubstituted or substituted aryl, R' is hydrogen or alkyl with 1 to 6 carbon atoms and B is a pruine or pyrimidine base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted guanine, purine, substituted purine, cytosine, substituted cytosine, thymine, uracil, substituted uracil, adenine and substituted adenine.

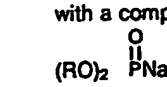
17. A process for preparing a compound of the formula



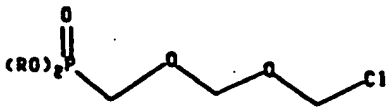
comprising reacting a compound of the formula



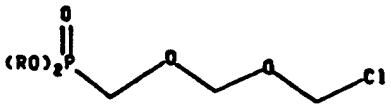
with a compound of the formula



to form a compound of the formula

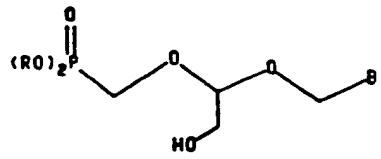


and reacting said

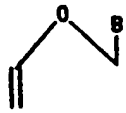


with a purine or pyrimidine base, wherein R is an alkyl having 1 to 6 carbon atoms and B is a purine or pyrimidine base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted guanine, purine, substituted purine, cytosine, substituted cytosine, thymine, uracil, substituted uracil, adenine and substituted adenine.

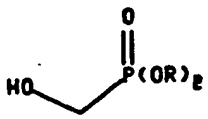
18. A process for preparing a compound of the formula



comprising reacting a compound of the formula

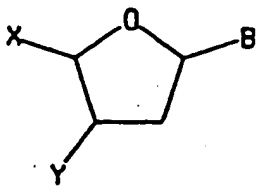


with a compound of the formula

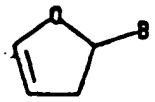


in the presence of a peracid, wherein R is hydrogen or alkyl with 1 to 6 carbon atoms and B is a purine or pyrimidine base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted guanine, pruine, substituted purine, cytosine, substituted cytosine, thymine, uracil, substituted uracil, adenine and substituted adenine.

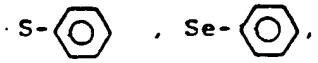
19. A process for preparing a compound of the formula



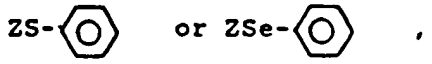
comprising reacting a compound



with X-Y, wherein
X is a halogen,
Y is

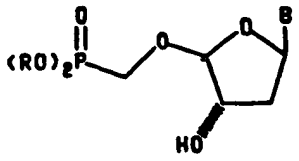


or a halogen,
and
X-Y is a halogen,

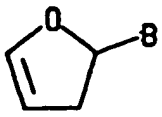


wherein Z is a halogen and B is a purine or pyrimidine base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted guanine, purine, substituted purine, cytosine, substituted cytosine, thymine, uracil, substituted uracil, adenine and substituted adenine.

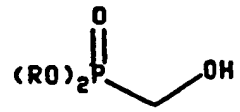
20. A process for preparing a compound of the formula



comprising reacting a compound of the formula



with a compound of the formula



with a peracid, wherein R is hydrogen or alkyl with 1 to 6 carbon atoms and B is a purine or pyrimidine base selected from the group consisting of xanthine, substituted xanthine, guanine, substituted guanine, purine, substituted purine, cytosine, substituted cytosine, thymine, uracil, substitued uracil, adenine and substituted adenine.

21. A process for preparing the pharmaceutical composition of claim 9 which comprises incorporating at least one compound according to anyone of claims 1 to 8 into a solid, liquid or gaseous diluent.

(19) Europäisches Patentamt
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(71) Applicant: **Bristol-Myers Squibb Company**
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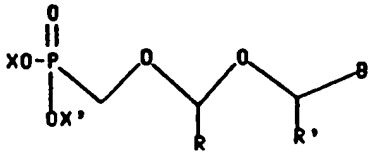
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(74) Representative: **Kinzebach, Werner, Dr. et al**
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W-8000 München 86 (DE)

(54) **Nucleoside analogs.**

(57) Compounds of the following formulas which have anti-tumor and anti-viral activity and are especially useful in treating viral infections, their compositions and use.

A phosphonomethoxymethyoxymethyl purine/pyrimidine derivative of the formula

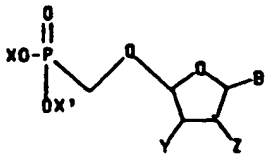


wherein X and X' are the same or different and are hydrogen or alkyl.

R and R' are the same or different and are hydrogen, alkyl, hydroyalkyl or R"CO-where R" is an alkyl and

B is a purine or pyrimidine base.

A 4'-phosphonomethoxytetrahydrofuranyl-1'purine-pyrimidine of the formula



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wherein X and X' are the same or different and are hydrogen or alkyl,

Y and Z are the same of different and are hydrogen hydroxyl or alkyl or Y + Z is an alkenyl, an epoxide or cyclopropyl, and

B is a purine or pyrimidine base.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 10 9066.2

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	WO-A-8 404 748 (SRI INTERNATIONAL) * abstract * ---	1,4,9,10	C07H19/10 C07H19/11 C07H19/20
D,A	FR-A-2 539 132 (CESKOSLOVENSKA AKADEMIE VED) * abstract * ---	1	C07H19/213 A61K31/70 C07D473/30 C07D405/04
D,A	JOURNAL OF MEDICINAL CHEMISTRY vol. 29, no. 5, 1986, WASHINGTON US pages 671 - 5 E.J.PRISBE ET AL. 'Synthesis of Antiherpes Virus Activity of Phosphate and Phosphonate Derivatives of 9-((1,3-Dihydroxy-2-propoxy)methyl)guanine.' * the whole document * ---	1,4,7-10	A61K31/505 A61K31/52 C07H21/04 C07F9/6561 C07F9/6571 C07F9/6512 C07F9/6558
P,A	WO-A-8 912 061 (MEDIVIR AB) * abstract * ---	2,9,10	
A	EP-A-0 044 527 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) * abstract * ---	7,9,10	
A	CHEMICAL ABSTRACTS, vol. 107, 1987, Columbus, Ohio, US; abstract no. 236377g, R.A.FOGUET ET AL. 'Process for the Preparation of 9-(2-Hydroxyethoxymethyl)guanine, used as an Antiviral Agent.' page 757 ;column 1 ; * abstract * & ES-A-519 857 (FERRER INTERNACIONAL S.A.) 16 March 1984 --- -/--	12	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07H
A61K
C07D
C07F

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29 MARCH 1993	SCOTT J.R.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

European Patent Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.

namely:

See sheet -B-

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid,

namely claims:

☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims,

namely claims:

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 10 9066

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	CHEMICAL ABSTRACTS, vol. 111, 1989, Columbus, Ohio, US; abstract no. 205325s, Y.KANEKO 'Light Fading Inhibitor for Color Photographic Material.' page 716 ;column 1 ; * abstract * & JP-A-01 055 556 (KONICA CO.) 2 March 1989	14	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
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D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims 1-11,13,15-21: Compounds of claims 1-8, pharmaceutical composition containing them, their processes of preparation and uses as medicaments; oligonucleotides of claim 11 and intermediates of claims 13 and 15 used to make compounds of claims 1-8

2. Claim 12: Intermediates of claim 12

3. Claim 14: Intermediates of claim 14